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YOUNG LAURELS: THE BRIEF LIVES OF JOHN IRVINE HUNTER, RENÉ LAENNEC AND JOHN KEATS.[1]

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THIS first Hudson-Deck Memorial Lecture, which I am honoured to give, is dedicated to the memory of two young physicians, Charles Burgoyne Hudson and Maurice Deck, who were members of the honorary staff of the Sydney Hospital. They were taken untimely from our midst, their careers just entered upon, and their great promise unfulfilled.

The early deaths of those we commemorate led me to think of doctors in history who had passed on while in mid-career. I propose, therefore, to review the lives of some young men who died in early life, and to speak of their contributions to medicine and literature. But first I must recall the lives and promising labours of those we remember today—Charles Hudson and Maurice Deck.

[1] The Hudson-Deck Memorial Lecture, delivered at Sydney Hospital during Sydney Hospital Post-Graduate Week, September, 1958.

Charles Hudson.

Charles Burgoyne Hudson was born on May 5, 1917, at Sydney. He began his education at Barker College, and then proceeded to "Shore", where he excelled both in school and on the playing field. His year book states that "he embraced medicine after a distinguished football, athletic and (alas!) debating career". At the Medical School he was a hard worker. Again quoting his year book: "Much continued effort was needed to overcome his conscientious objections to interference with his dissecting activities, but soon he learnt to appreciate the many other worth-while aspects of 'Varsity life'." At graduation in 1940, he gained the Clayton Memorial Prize for Medicine and Clinical Medicine. He was appointed resident medical officer at the Sydney Hospital, but left after one year to join the medical service of the Royal Australian Air Force, in which he served for four and a half years.

His leadership and capacity must have been recognized in the Air Force, because he was chosen to lecture on chemical warfare and blood transfusion. The latter was a subject which appears to have interested him particularly, as in 1943 he published a paper in THE MEDICAL JOURNAL OF AUSTRALIA entitled "A Rapid Method for Cross Matching of the Blood of Donor and Recipient".

In 1944, he was successful in the membership examination of The Royal Australasian College of Physicians, and

soon after his demobilization in 1946 he was appointed an assistant physician at Sydney Hospital.

Entering general practice in Wahroonga, he was immediately successful, and his ability, industry and warm, sympathetic nature were soon reflected in the large numbers of patients who turned to him for their medical care. Continuing his honorary work at Sydney Hospital, and later at the Hornsby District Hospital, he soon established a reputation as a physician, and to continue his career he left general practice in 1955 and became established as a consulting physician in Macquarie Street. Here, too, his success continued, and, had he lived, he would soon have accumulated a large practice. At the

FIGURE I.
Charles Burgoyne Hudson.

hospital he worked for the clinical advancement of our school, and his enthusiasm stimulated everybody. His leadership among the assistant physicians was acknowledged, and his counsel, always wise and authoritative, was frequently sought.

Charles Hudson was closely associated with me in practice both at the hospital and in "the Street", and a more delightful colleague could not be imagined. His integrity and charm of personality made our association a constant pleasure, and of his help and support, I keep a most grateful memory.

In the face of the malady which struck him down, he maintained a most courageous attitude. When all investigations had been completed, he refused to discuss it further with me, saying that he was doing what was necessary, and in any case "it might worry him".

Maurice Deck.

Maurice Feild Deck was born in Mosman on January 11, 1911. After his preliminary schooling at the Mosman Preparatory School, he proceeded to Sydney Grammar School, and thence to the Medical School in 1929. On graduation at the end of 1934, he was appointed to Sydney Hospital. He left at the end of his junior year to fit himself for practice by spending six months at the Royal Hospital for Women, Paddington, and six months at the Royal Alexandra Hospital for Children. He married in February, 1937, and went into practice at Bowraville, on the north coast of New South Wales, where he remained for over four years. On the outbreak of war he volunteered for service, but was rejected on medical grounds.

In 1942, he began a post-graduate year at the Prince Henry Hospital with Dr. S. A. Smith, then in charge of the medical post-graduate division, and in September of

FIGURE II.
Maurice Feild Deck.

that year he passed the membership examination of The Royal Australasian College of Physicians.

In 1943, he again entered general practice in Roseville, and also obtained appointment to the medical out-patient department of Sydney Hospital as a clinical assistant. In 1949, he was appointed Honorary Assistant Physician to Sydney Hospital, and took rooms in Macquarie Street, but continued to practise at Roseville until 1954, when he left general practice to devote his whole time to consulting and hospital work.

Maurice Deck was a quiet, unobtrusive but most sincere man, who was passionately devoted to the care and welfare of the patients in his charge. Stories are still told of his numerous acts of kindness and thoughtfulness, such as borrowing a projector and arranging, on Christmas Day, a picture show at the local hospital for the chronically ill and bed-ridden. He was known to be deeply religious, but made no parade of his piety. He preferred that his Christianity should be of the practical kind and, following the example of its founder, "he went about doing good". Ill health had dogged his life for many years, and when the unforeseen complication predicted an early end, he was calm and he was prepared. The accompanying portrait (Figure II) was taken while he was following his favourite relaxation of sailing. He was happiest when in his boat, and he loved to share this pleasure with his friends.

John Irvine Hunter.

One of the most remarkable young men of medicine that our Medical School has ever produced was John Irvine Hunter, and I think it proper that on this day—when we are commemorating young men—those who had not the privilege of knowing him should be reminded of his work, and of his genius.

He was born at Bendigo on January 24, 1898, and began his education at the Albury District School, transferring to the Fort Street Boys' High School at the age of fifteen. At both schools his unusual mind was apparent.

Entering the Medical School with a bursary in 1916, he was *proxime accessit* in the Renwick Scholarship for general proficiency in first year. After this he carried all before him—the prizes for botany and zoology, the John Harris prize for anatomy and physiology in third year, the Caird prize for pathology and operative surgery in fourth year, in fifth and final year the Hinder prize for clinical surgery, and the Sandes prize for an essay on "Abdominal Pain and Associated Reflex Phenomena" (later published in THE MEDICAL JOURNAL OF AUSTRALIA). He graduated M.B. and Ch.M. with first-class honours and the University Medal. Surely an impressive record! The Professor of Anatomy, J. T. Wilson—affectionately known to all as "Jummie"—had recognized Hunter's capacity, and in July, 1920, three months after graduation, he was appointed Lecturer in Introductory Anatomy. Soon afterwards Professor Wilson resigned to take the Regius Chair of Anatomy at Cambridge, and the late Dr. F. A. Maguire was appointed Acting Professor of Anatomy, and Hunter, Associate Professor, in recognition of his "remarkable aptitude for teaching and research work". All this within a few months of graduation! The students, of whom I had the privilege to be one, soon discovered that his lectures and demonstrations were inspired. I can remember this slim, dark-eyed young man, the lock of black hair falling across his forehead, fired with enthusiasm for his subject, pouring forth words in a soft yet vibrant voice, and literally making the dry bones live. After the lecture, too, no question was too trivial to receive his consideration and patient answer, and time was never too short for explanation.

In addition to teaching, he continued research work, and the investigation of certain interesting morbid anatomical specimens. One of these was an early primary ovarian pregnancy, in which he demonstrated unequivocally that a decidual reaction could take place in the ovary. He presented this work in a paper delivered to the New South Wales Branch of the British Medical Association. It created a great impression, not only for the matter, but for the manner of its presentation—the clarity, mastery of detail and authority with which genius can inform a subject. He received an ovation, and his reputation beyond the confines of the University, already known, was now enlarged.

The University authorities, recognizing Hunter's capacity, but also his age of twenty-three years, decided to keep the Chair open and to send him abroad to allow him to grow a little older and more mature, and his genius to flower. He spent part of the eighteen months abroad working at Cambridge with his old teacher and friend "Jummie" Wilson, and part of the time with Professor Grafton Elliot Smith at University College. He returned to the appointment of Challis Professor of Anatomy at the University of Sydney at the age of twenty-five.

On May 7, 1924, the Senate conferred on John Irvine Hunter the degree of doctor of medicine with first-class honours, the University Medal and the Ethel Talbot Prize for a thesis on the forebrain of the kiwi—a work of outstanding merit.

John Hunter is perhaps best known to you for his work with the late Dr. N. D. Royle on the subject of spastic paraplegia. Royle, an orthopædic surgeon, was seeking a means of relieving spasticity, and Hunter, regarding it as a problem in disordered physiology, aided the work with his usual enthusiasm and advice and accumulated experience. The role of the sympathetic supply of voluntary muscle in the maintenance of postural tone was established, and Royle carried out the first division of the white rami for the relief of spasticity in the human subject. Hunter never ceased to give Royle precedence in this work; but from this time onwards he became more than ever absorbed in the physiological problem. Naturally, the practical application of this research received great publicity, and aroused the interest of Dr. "Willie" Mayo, of the famous clinic, and Dr. Franklin Martin and other representatives of the American College of Surgeons, who visited Sydney in October, 1924. They invited Hunter and Royle to give the John B. Murphy Oration at the meeting of their College in New York that

FIGURE III.
John Irvine Hunter.

month. This was a great honour, not only to these men, but to this country. Hunter was the central figure in this great meeting of surgeons. Unhappily, it was the last act in the academic life of this brilliant man. He crossed to England late in November, became ill on December 2, and died in University College Hospital on the evening of December 10, 1924, of enteric fever, at the age of twenty-six years.

No memoir of this remarkable young man of medicine, and man of genius, would be complete without reiteration of his essential simplicity, his modesty and his charming and lovable nature. His was the charity of St. Paul that "suffereth long, and is kind; charity envieth not; charity vaunteth not itself, is not puffed up; charity never faileth"; and it is appropriate to continue this passage here: "but whether there be prophecies, they shall fail; whether there be tongues, they shall cease; whether there be knowledge, it shall vanish away". What a cruel blow to medicine in Australia, and the world, that the knowledge, actual and potential, of this "teeming brain" should vanish away!

René Théophile Hyacinthe Laennec.

In a plain granite house on the quay of the port of Quimper, thirty miles south-east of Brest, was born on

February 17, 1781, René Théophile Hyacinthe Laennec, who was destined to become a famous young man of medicine. His father was a member of the Bar, and many of his family had been lawyers. Théophile, as he was called, was the first child, and when his mother died two days after the birth of her fourth, who also died, he and his brothers were sent to the care of an uncle in Nantes, as his father, though charming and cultured, was irresponsible, and unable to cope with the education of his children. The father's brother, Guillaume, who was a doctor and to whom the boys were now entrusted, was a most intelligent man, a classical scholar, a good speaker and writer, and had a profound influence on the development of the future physician. At this time Guillaume was 40 years of age, had studied in England under Hunter, and was Rector of the University of Nantes. Guillaume, his wife and mother-in-law, his three children, his nephews, his servants, a parrot and a dog, made up the household. Théophile appears to have become an immediate favourite, and showed an inherited instinct by writing poetry at the age of eleven. Nantes felt the full blast of the French Revolution. The guillotine, and cannon with chain shot, slaughtered thousands. Having access to their aunt's cottage in the country, the boys may have missed much of this horror, although we read of the two little boys being pulled out of bed in the small hours of the morning of June 8, 1794, by the orders of Robespierre, to take part in the *Fête de l'Être Suprême*, which began with cannon fire at 5 a.m., Théophile—then thirteen—wearing a sword.

His uncle William appears to have had a great influence upon his nephew. He encouraged him, stimulated him to work hard, which he did naturally, and provided him with the funds denied him by his negligent father.

In September, 1795, at the age of fourteen and a half years, Laennec began the study of medicine in the *Hôtel-Dieu* at Nantes. At the same time he was appointed "Military Surgeon of the Third Class", and was probably attached to a hospital with his uncle—this is surely an indication of the turbulent nature of the times. His active mind found time to become interested in such varied activities as botany, nature study, Greek, dancing and music, which he loved, and he learnt to play the flute well.

He left the medical school in Nantes in 1801, and entered *L'École de Médicine* in Paris in May of that year. His passion for medicine absorbed his whole mind, and his genius became obvious. He showed that "love of labour and perseverance" which Hippocrates said was necessary, among other things, for the acquisition of a competent knowledge of medicine. However, his health now began to give trouble and nervous symptoms, sleeplessness and asthma appear in his record. He thought of abandoning his career more than once for a country life, which he loved, but his profession proved the greater attraction. He elected to study at *La Charité*, the hospital headed by Corvisart, Napoleon's personal physician, who is known as one of the founders of pathological anatomy, and an advocate of Auenbrugger's method of percussion. Corvisart wrote particularly on diseases of the heart and lungs, and may have interested Laennec in this field. The school at *La Charité* based the study of medicine upon morbid anatomy, whereas *La Salpêtrière*, the other school, adopted a more theoretical approach to the subject. Laennec may have been attracted to the *Charité* also because of his admiration of Marie-François Bichat, who is another of the brilliant young men of medicine. Bichat died in 1802 at the age of thirty-one, and has been called "the creator of descriptive anatomy"—which is remarkable, in view of his brief life.

Laennec's industry is reflected in his notes, which were copious. During his first three years at the *Charité* he took case histories of nearly 400 patients, in minute detail.

Baron Guillaume Dupuytren was working on morbid anatomy at this time, and for a while he and Laennec were associated; but Dupuytren was apparently a hard and most difficult man, though eminent as a diagnostician, teacher, operator and pathologist. A controversy with him over a priority of classification piqued the sensitive Laennec, and they were estranged for a long time. The classification of disease appears to have absorbed a great deal of the student's time in Paris at that time. Papers now began to appear in profusion from the pen of the young physician, one being on hydatid cysts, which, for the first time, he showed were of parasitic origin.

Bichat having died, Laennec began to give lectures on morbid anatomy. Dupuytren also lectured on this subject, and their rivalry was intense. Dupuytren's lectures were said to be the more brilliant and drew the larger audiences; but Laennec's made a great impression and added to his growing reputation. He would begin, it is said, in a gentle low voice, but would end—like Epaminondas—in a torrent of eloquence.

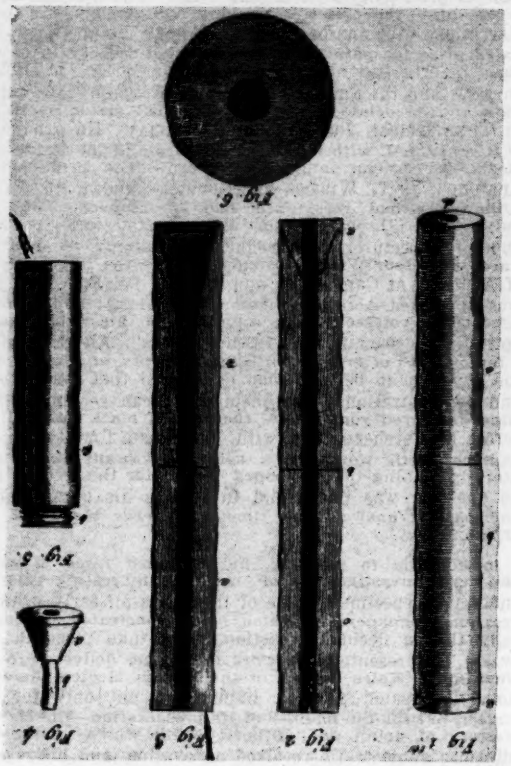

FIGURE IV.

Diagram of Laennec's first stethoscope or *cylindre*, from his *"Traité de l'auscultation médiate"*, 1826.

In September, 1803, he won the *Grands Prix* in both surgery and medicine, and in July, 1804, he became a member of the *Société de l'École de Médecine*—a great distinction for one so young. By this time he had become one of the leading morbid anatomists in Paris; but it may be said that he breathed life into the subject by correlating the symptoms of the patient with the post-mortem findings.

There must have been plenty of clinical and autopsy work in Paris in those years, as Paris was full of sick and wounded soldiers from the Napoleonic Wars, and typhus was raging.

You are no doubt familiar with Laennec's account of the incident which led to his introduction of the stethoscope or *cylindre*, or *baton*, as he sometimes called it, but I will read it again:

> In 1816 I was consulted by a young woman presenting general symptoms of disease of the heart. Owing to her stoutness little information could be gathered by application of the hand and percussion. The patient's

age and sex did not permit me to resort to the kind of examination I have just described (i.e., the direct application of the ear to the chest). I recalled a well-known acoustic phenomenon: namely, if you place your ear against one end of a wooden beam the scratch of a pin at the other extremity is most distinctly audible. It occurred to me that this physical property might serve a useful purpose in the case with which I was then dealing. Taking a sheaf of paper I rolled it into a very tight roll, one end of which I placed over the precordial region, whilst I put my ear to the other. I was both surprised and gratified at being able to hear the beating of the heart with much greater clearness and distinctness than I had ever done before by direct application of my ear.

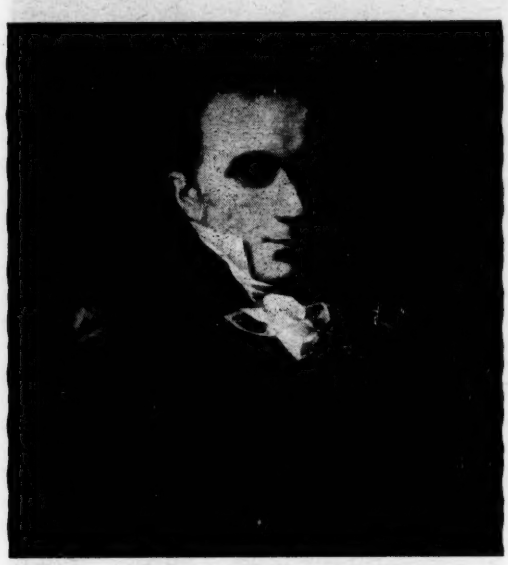

FIGURE V.
René Théophile Hyacinthe Laennec. From a portrait by Dubois, 1812.

Laennec continued to improve his new instrument, and by constant practice with it became familiar with the sounds heard. He then correlated them with post-mortem appearances. On February 28, 1818, he read before the Academy of Sciences a paper entitled "A Memorandum on Auscultation by the Aid of Divers Acoustic Instruments Used as a Means of Examination in Disease of the Thoracic Viscera and Particularly in Pulmonary Phthisis". On May 1 and 14, June 11 and July 9, 1818, he lectured before the Faculty of Medicine on the same subject. Finally, in August, 1819, he published his observations in that masterpiece "De l'auscultation médiate", or "A Diagnostic Treatise on Pulmonary and Cardiac Disease, Based Principally on the New Method of Examination". Hale White writes:

> In this astonishing book there occur perfect, precise and original descriptions of clinical symptoms and post-mortem appearances, neither too long nor too short, for the most part as true now as in the day they were written. . . . his book . . . was beautifully written, it is a pleasure to read it, the descriptions are accurate and clear cut without the encumbrance of superfluous words. It has become and will remain a classic.

Here, for example, is a passage from his book:

> Dilatation of the bronchi is invariably the outcome either of chronic catarrh or of some other malady capable of producing long and violent fits of coughing recurring over a considerable period of time. Of all diseases whooping-cough is perhaps more often than any other responsible for the organic lesion under discussion.

The book was an immediate success, and came as a revelation to the physicians of the day.

Laennec has been described as a small, attenuated, bony figure of a man, with prominent cheek bones, hollow cheeks, thin nose and lips, calm reflective blue-grey eyes, a long head covered with carelessly combed abundant chestnut hair, who was not handsome, but not plain, and whose face showed much distinction and intelligence. He began private practice in 1805. In his first year he earned 150 francs, in the second 400; after that his income increased rapidly, until in 1813 he was a busy, fashionable physician. Meanwhile he had continued clinical research, lecturing and writing so intensively that in 1818 his health broke down, and he was forced to take a long holiday. Next year, shortly after publication of his book, he became ill again, with cough, dyspnœa, anorexia and weakness, and great depression. It is obvious he was suffering from pulmonary tuberculosis, but was denied the *spes phthisica*.

In spite of his meteoric career and brilliant prospects, he determined to leave Paris for good, and so at the age of thirty-nine he set out for his native Brittany, and his house, Kerlouarnec, not far from where he was born. Two years later, however, in greatly improved health, he listened to the clamour for his return. He was anxious, moreover, to be in the medical world again, and a second edition of his book would soon be needed. He therefore determined to return to Paris, which he did in November, 1821. He began clinical lectures again almost at once, and one of his students at this time was Thomas Hodgkin, of Guy's Hospital, whose name is known to us all.

In 1822, Laennec was elected Professor and Royal Lecturer at the College of France, and was probably the first distinguished tenant of this office since its foundation in 1542. After him, however, great names appear — Majendie, Claude Bernard, Brown Séquard, *inter alia*.

On January 24, 1823, he was elected a member of the Academy of Medicine, having previously been an associate, and on August 22, 1824, he became a Chevalier of the Legion of Honour.

Laennec was always so refreshed and reinvigorated by his enforced vacations in Brittany that he championed the fresh-air treatment of respiratory disease in general, and of phthisis in particular. In addition, he thought that some virtue might emanate from the seaweed of his native shores. Consequently, seaweed was scattered round the beds of some of his patients in Paris; to others he gave infusions of seaweed—of course without effect.

He was appointed physician to the Duchess of Berry, and his practice became enormous, obliging him to restrict his work to consulting practice only. Once again, the strain of clinical and literary work took its toll, and he was forced to retire to Brittany for the second and last time. The second edition of his book appeared just as he left Paris, to die, in the summer of 1826. By this time he was suffering from tuberculosis in a terminal phase. He died at his beloved Kerlouarnec on August 13, 1826, at the age of forty-five, from the disease which has been termed one of the infirmities of genius.

As is usual, his discoveries were derided and ridiculed. His chief assailant was Broussais—one-time soldier, naval medical officer, medical hospital physician, and finally Professor of Pathology of the University of Paris. Garrison, the medical historian, describes Broussais' methods of teaching as Napoleonic, and his therapeutics as sanguinary.

Laennec triumphed over his critics because he worked in the wards of the hospital, where students and interns saw the accuracy of his observations and the truth of his statements.

It is pleasing to note that his work was appreciated more in England than in any other country. An order was issued by the British Admiralty that naval surgeons were to familiarize themselves with the use of the stethoscope, and the famous treatise was partially translated into English as early as 1821.

Do we physicians ever stop to think what we owe to this young man of medicine? Clear descriptions of disease of heart, lung and liver, and an instrument—these were his gifts. The student who proudly swings his stethoscope, or hangs it round his neck, regards it almost as a badge of rank. But it is not merely a symbol of our calling—it is a very necessary tool of trade. Electronics are all very well, but after the eyes and the hands come the ears, with our modification of Laennec's *cylindre* to aid them.

FIGURE VI.

René Théophile Hyacinthe Laennec. From a portrait drawn by himself about 1820.

John Keats.

On October 31, 1795, John Keats was born in London, in rooms over, or beside, the stables and coach houses of the Swan and Hoop Inn on Finsbury Pavement, near the site of the present Liverpool Street station. He was destined to become a young man of medicine, in a form acceptable in his day, but never to practise it. A far greater destiny, however, was in store for him—to join the immortals of English poetry.

His father had come to London to seek employment, but from what part of England is unknown, and had been engaged as an ostler by Mr. John Jennings—the keeper of the Swan and Hoop—who has been described as "a man of generous spirit, trusting, easily deceived". However he appears to have been so taken with his employee that, some years later, he put no obstacle in the way of his marriage to his only daughter Frances, a gay and pretty girl, aged nineteen. Their first child, John—the future doctor and poet—was a premature infant, born at seven months. Naturally his mother's love of a life of gaiety has been blamed for this, but she was a good wife and mother, and John, her favourite son, worshipped her.

John Keats was sent to John Clarke's School at Enfield, a middle-class school, where sons "of professional men of moderate income, small merchants, and better class tradespeople" were educated. The choice of this school was fortunate, and was destined to have a great influence, directly and indirectly, upon the development of Keats's literary flair. One of the masters was Charles Cowden Clarke, a son of the principal, a discerning young man and a lover of literature. He soon recognized the genius of the new pupil and encouraged his reading. He was later to introduce him to Leigh Hunt and a London literary circle. It was he, also, who put into John's hands the 1616 folio edition of Chapman's Homer—an event immortalized for us in the sonnet "On First Looking into Chapman's Homer". Master and pupil were intoxicated by this book, and sat through the night, reading it till dawn.

Unlike the usual conception of one destined to become a poet, Keats wes quarrelsome and easily provoked and loved fisticuffs. One of his contemporaries said that fighting was "meat and drink to him". On the other hand, he was witty, amusing, a leader among his fellows

FIGURE VII.

John Keats.

and an exceedingly good-looking boy. He was naturally clever, and read avidly everything he could lay his hands on. In his last year at school he won four prizes—three books and a medal.

His father having been accidentally killed, the Keats children—three boys and one girl—were entrusted to a guardian, a business man named Richard Abbey. At the end of their schooldays, he was able to place the brothers, Tom and George, in his office; but John was a problem. What could be done with this obviously talented boy who was always either reading or scribbling verses? Abbey did not understand him, but in the end arrived at a satisfactory compromise. He decided to apprentice him to a surgeon, as he was unable, or unwiling, to send him to Edinburgh to become a physician, a long and costly process. Keats was apprenticed to Dr. Hammond, in Edmonton. The average premium for such apprenticeship was about £40, but the amount rose if the surgeon had a big reputation and many applicants for apprenticeship. The apprentice did all the dirty work of the practice and accompanied his master everywhere—usually to hold his horse. Fortunately, Edmonton was not far from Enfield, and Keats was still able to maintain contact with his former teacher and literary mentor—Charles Cowden Clarke—who continued to guide his reading and introduced him to Shakespeare and Spenser, among others. Spenser's "Faery Queen" dazzled Keats, and had much to do with the development of his future style.

As was mentioned before, Clarke introduced Keats to Leigh Hunt, a literary figure of the time and editor of

The Examiner. Through Hunt, Keats met many of the literati of the day. With his mind full of books, poetry, and sayings and doings of writers and poets, Keats found his apprenticeship irksome. His turbulent nature soon found cause for a dispute, in which he says he even raised his hand against Dr. Hammond. The indentures were broken by common consent. No doubt the doctor felt relieved to be rid of him, and John set off for London and Guy's Hospital, where he entered as a medical student on October 1, 1815. Here Keats attended lectures by Astley Cooper, then at the height of his powers as anatomist and surgeon. He must have recognized that the new student was exceptional, as he was at pains to put him in the care of a namesake—George Cooper—who was one of his dressers. George Cooper took Keats to live with him in his lodgings over a tallow chandler's shop, which he shared with two other students, Stephens and Mackereth. Stephens was a man of parts; he loved literature and even wrote verses himself. He is credited with the introduction of creosote into medicine and was, I think, the founder of the famous ink firm of that name.

Keats must have had great charm and personality. Stephens recognized his quality and admired him greatly. He has left us pictures of the young student sitting in his favourite seat in the window—Keats's place, as it was called—reading or dreaming. Sitting there one evening he recited to Stephens: "A thing of beauty is a joy for ever." "What do you think of that?" he asked. "That it will live for ever", Stephens replied. Time has proved him right.

Apart from his absorption in literature, Keats appears to have been a normal medical student, and a good companion. He was interested in cards, and the theatre and the ordinary amusements of a student of that time.

In July, 1816, Keats was examined for his final diploma of the Society of Apothecaries. Much to the surprise of his fellow students—who, no doubt, thought him an idler, always writings verses—he passed. His native ability must have stood him in good stead, because, on his own admission, he was most inattentive at lectures. "The other day", he said, "during the lecture, there came a sunbeam into the room, and with it a whole troop of creatures floating in the ray; and I was off with them to Oberon and fairyland." Although he had passed his examination, he still continued to work at Guy's Hospital till one day he had to open a man's temporal artery. No doubt this was one of the methods of bleeding. He must have realized at that moment that his heart was not in medicine. Speaking of it, he said: "On reflecting what had passed through my mind at the time, my dexterity seemed a miracle, and I never took up the lancet again." This ended his active association with medicine. Henceforth he devoted himself entirely to his muse of "eternal poetry", and the next four years were to be his most productive. He was now twenty-one, and exceedingly good-looking, with large and lustrous eyes. Hayden, the painter, said "he seemed, and looked, conscious of a high calling". He was broad shouldered, but only five feet in height. Naturally he was always called "little Keats". Middleton Murray, an authority on Keats and the author of "Keats and Shakespeare", said "Had Keats been six inches taller, the history of English literature in the nineteenth century might have been different." It is interesting to reflect that our little colleague of the early nineteenth century should have been thought worthy of comparison with the Elizabethan giant. But an authority other than Middleton Murray has considered them worthy of comparison also. No less a person than Matthew Arnold, commenting on Keats's statement, "I think that I shall be among the English poets after my death", said "*He was*; he is with Shakespeare." It is interesting to recall that both Shakespeare and Keats often wrote of sleep, a subject of importance to doctors. Shakespeare's lines of Macbeth, of course, are well known:

> . . . the innocent sleep,
> Sleep that knits up the ravell'd sleave of care,
> The death of each day's life, sore labour's bath,
> Balm of hurt minds, great nature's second course,
> Chief nourisher in life's feast.

Wonderful and wise; but listen to this verbal lullaby written by the young man of medicine:

> O soft embalmer of the still midnight!
> Shutting with careful fingers, and benign
> Our gloom-pleased eyes, embower'd from the light,
> Enshaded in forgetfulness divine!
> O soothest sleep! if so it please thee, close,
> In midst of this thine hymn, my willing eyes,
> Or wait the amen, ere thy poppy throws
> Around my bed its lulling charities;
> Then save me, or the passed day will shine
> Upon my pillow, breeding many woes;
> Save me from curious conscience, that still lords
> Its strength for darkness, burrowing like a mole;
> Turn the key softly in the oiled wards,
> And seal the hushed casket of my soul.

This example of Keats's wizardry with words should be a cure of insomnia if, instead of counting sheep, it could be learnt and recited by the sufferer.

Keats as a boy had sat by his mother's bedside and seen her die of tuberculosis. After his graduation he had nursed his brother Tom, whom he also loved, till his death in 1818 from the same disease. We may imagine his consternation when, on a bitter February day in 1820, after riding on the outside of the Hampstead coach without a coat, he had his first hæmoptysis. "That drop of blood", he said to his friend Brown, "is my death warrant"—and so it proved to be. "Phthisis ab hæmoptoe" the older writers called this first sign of the disease—under the misapprehension that the hæmorrhage into the lung tissue was responsible for the destruction and cavitation of that organ. Just a year later, on February 23, 1821, Keats died in Rome, whither he had travelled on the advice of his doctors in a vain attempt to recover his health. He was buried in the English cemetery, among the ruins of the old Aurelian wall, and at his request, the epitaph on his tomb is:

> Here lies one whose name was writ in water.

Life is inscrutable and cruel. It is impossible to avoid a thought of the good which our young colleagues might have done had they been spared; of the heights to which those we have discussed might have risen had they lived; and of many more besides. For, in thinking of young men of medicine, other names spring to one's mind—Walter Reed, of yellow fever fame; Dutton, discoverer of the *Trypanosoma gambiense* and the spirochaete of central African relapsing fever, the *Spirochæta duttoni*—dead at thirty-one; Tom Parkinson, of our own school, who died at the age of twenty-six, while investigating plague.

The loss of young men of medicine is the more regrettable, because it is to them that older men must look to continue the labours of teaching and of research, and to provide ideas for the future. As age advances and commitments increase, the minds of all but the exceptional lose their momentum. They become more static, and somewhat confused by the pace of life and the progress of medicine. "The world is too much with us; late and soon, getting and spending we lay waste our powers", said Wordsworth; and so to the young men, who have resilience, we must look for advances.

> To you from falling hands we throw
> The torch; be yours to hold it high.

Shelley, who was soon to be buried beside our doctor-poet, John Keats, immortalized him in his elegy, "Adonais". I should like to borrow some of the lovely lines from this poem (changing the singular to plural in a few words) since they may be of comfort to the relatives and friends of Charles Hudson and Maurice Deck, of whom we are thinking today:

> They have outsoared the shadow of our night;
> Envy and calumny, and hate and pain,
> And that unrest which men miscall delight
> Can touch them not, and torture not again;
> From the contagion of the world's slow stain
> They are secure . . .

CLINICAL AND EXPERIMENTAL STUDIES ON BRETYLIUM TOSYLATE, A NEW HYPOTENSIVE AGENT.

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BRETYLIUM TOSYLATE[1] ("Darenthin", Burroughs Wellcome) is a new type of hypotensive agent, which in animals selectively blocks the post-ganglionic peripheral sympathetic (adrenergic) nervous system, but does not have any blocking effect on the parasympathetic nervous system and does not depress the central nervous system (Boura, Copp *et alii*, 1959). In humans, bretylium tosylate produces hypotension without any evidence of parasympathetic blockade (Boura, Green *et alii*, 1959).

A serious defect of ganglion-blocking agents used in the treatment of hypertension has been their parasympathetic-blocking activity, manifested particularly by dryness of the mouth, constipation, blurring of the vision and impotence. These side effects are often sufficiently severe to restrict the use of these drugs, and occasionally may even prevent their use. Initial clinical reports (Boura *et alii, locis citatis*) suggest that bretylium tosylate is a potent hypotensive agent without such drawbacks, and that it may therefore be of value in the treatment of hypertension. This paper describes the clinical findings of a preliminary trial of bretylium tosylate in the treatment of hypertension. In addition, it presents the findings of experimental studies of the action of the drug on autonomic nervous activity in normotensive and hypertensive human subjects, and in normotensive animals.

MATERIALS.

Bretylium tosylate ("Darenthin") is the abbreviated name of the *p*-toluene sulphonate salt of the benzyl quaternary ammonium base (Figure I), which was the compound used in this work, dispensed for oral consumption in 200 mg. compression-coated tablets, each of which contained 112 mg. of base. For convenience, the doses mentioned refer to the weight of toluene sulphonate salt, bretylium tosylate.

In the animal experiments, bretylium tosylate in aqueous solution, calculated as 10 mg. base per millilitre, was injected intravenously.

Methods.

In humans, blood pressure was measured by auscultation, the standing blood pressure being measured after 30 seconds to one minute in the erect position.

In animal experiments, mongrel male or female dogs, weighing 10 to 15 kg., were anæsthetized with "Nembutal" administered intravenously, and given heparin in a dose of 100 units per kilogram. A rigid "Polythene" catheter was passed into the aorta via a femoral artery and tied in position. The free end was connected to an electromanometer[2] attached to a recording camera. A brachial vein was cannulated for the administration of drugs. The electrocardiogram was also continuously recorded.

CLINICAL INVESTIGATIONS OF HYPERTENSIVE SUBJECTS.

Sixteen patients (12 men, four women) have been treated with the drug. Five patients whose hypertension had proved difficult to control satisfactorily with ganglion-blocking drugs (pentolinium, mecamylamine, pempidine) during the past five years have been given the drug continuously for five months. The remaining 11 have been treated with bretylium tosylate for one to four months. Seven had previously been treated for hypertension for one to three years with ganglion-blocking drugs, reserpine and chlorothiazide. In five of the seven the results of this treatment had been satisfactory. Four patients had had no previous hypotensive therapy. Eight patients commenced treatment during their stay in hospital; the remaining eight were out-patients.

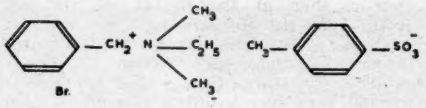

FIGURE I.
Bretylium tosylate ("Darenthin").

Effects of a Single Dose of Bretylium Tosylate.

A hypotensive effect was observed in all 16 patients, the minimum dose required to produce a fall in blood pressure varying from 100 mg. (half a tablet) to 800 mg. (four tablets), with nine subjects responding adequately to 200 or 300 mg.

A minimally effective dose of the drug was followed by a slight fall in blood pressure in the supine posture, but a marked fall in the erect position, reaching a minimum at four hours (Figure II). The fall in blood pressure

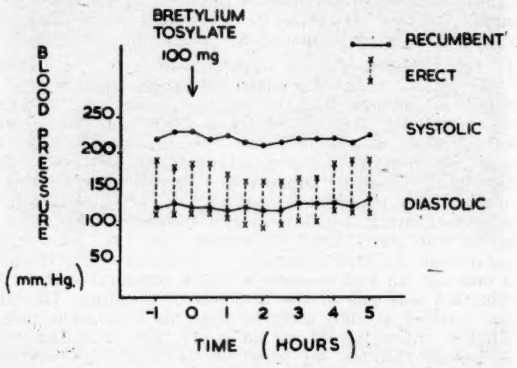

FIGURE II.
Effect of 100 mg. of bretylium tosylate on a subject with essential hypertension.

was not accompanied by any change in the pulse rate. A larger dose in the same subject was followed by a larger fall in the systolic and diastolic pressures, which commenced after 30 minutes, reached a minimum after approximately four hours and returned to the original level after about seven hours (Figure III).

In two subjects a dose of 600 mg. produced a slight fall in blood pressure in the supine position, but no greater fall in the erect posture.

When sufficient bretylium tosylate was given to produce a hypotensive effect, a simultaneous and parallel fall in systolic and diastolic pressures occurred (Figure III). As the dose was increased, there was a further fall in systolic and diastolic pressures. This is in contrast to our experiences with ganglion-blocking agents. With these we have found that a small dose reduced the systolic pressure, but had little effect on the diastolic pressure. With larger doses a sudden marked fall in diastolic pressure occurred, with severe postural hypotension.

The graded response to bretylium tosylate, with a parallel fall in both systolic and diastolic pressures, resembles the response that sometimes occurs with reserpine.

[1] Bretylium tosylate ("Darenthin", Burroughs Wellcome), (N-o-bromobenzyl-N-ethyl-N-ethyl : N : N-dimethylammonium *p*-toluenesulphonate).

[2] New Electronic Products Ltd. (London).

Maintenance Dosage.

The duration of an effective single dose is limited to about five hours, and as cumulation does not occur, three and often four spaced effective single doses are required daily to maintain the blood pressure at a satisfactory level. A given dose taken before a meal often produces a greater fall in blood pressure than the same dose taken after meals, and the drug was therefore given at 7 a.m., 11 a.m., 4 p.m. and sometimes 9 p.m. also. However, with two subjects it was noted that what had been found to be a satisfactory dose in the afternoon—for example, 200 mg.—was too great as an early morning dose, producing severe postural hypotension, and in this respect the action of bretylium tosylate resembles that of ganglion-blocking agents (Hayden, 1954). Some of these points are illustrated in the following case records.

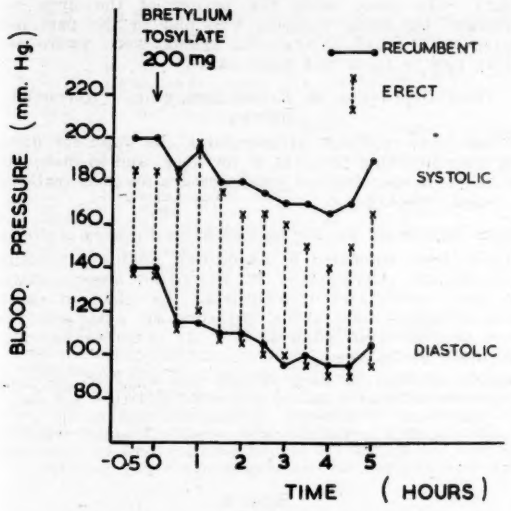

FIGURE III.
Effect of 200 mg. of bretylium tosylate on the same subject.

CASE II.—A female patient, aged 52 years, presented in December, 1958, with pontine thrombosis, and a blood pressure of 190/120 mm. of mercury in the recumbent position. She was treated with reserpine and chlorothiazide until July, 1959, but these drugs produced only a slight fall in blood pressure. Since July, 1959, she has been treated with bretylium tosylate. There is a good response to 200 mg. (Figure III), and her hypertension is adequately controlled with 200 mg. three times a day. However, severe postural hypotension was experienced in the morning, and the morning dose was reduced to 100 mg. She feels well, and is relieved of the tiredness and depression noticed when she was being treated with reserpine. She has occasional headaches, and occasional nasal congestion.

CASE VIII.—A male patient, aged 28 years, presented in August, 1958, with severe hypertension, his blood pressure being 240/140 mm. of mercury in the recumbent position. No retinal or renal complications were present. He was treated with mecamylamine until July, 1959, and subsequently with bretylium tosylate. Doses of up to 600 mg. did not lower the blood pressure, but at present it is satisfactorily controlled on 800 mg. four times a day, together with one gramme of chlorothiazide per day. No side effects have been noted.

Potentiation of the Hypotensive Action of Bretylium Tosylate by Chlorothiazide.

Five patients were treated with bretylium tosylate and chlorothiazide together, and chlorothiazide in a dose of one gramme per day potentiated the hypotensive action of bretylium tosylate. This effect, which may convert an ineffective dose of bretylium tosylate into an effective one, is reversible (Figure IV). In two cases, chlorothiazide added to an effective dose of bretylium tosylate produced a sudden fall in blood pressure with severe postural hypotension.

CASE X.—A female patient, aged 48 years, presented in July, 1959, with severe hypertension (blood pressure 280/180 mm. of mercury in the recumbent position) and cerebral thrombosis. She was initially treated with hexamethonium bromide by intramuscular injection and later stabilized with bretylium tosylate (200 mg. three times a day) and chlorothiazide (1 gramme per day). When she was next examined as an out-patient two weeks later, her blood pressure was 240/140 mm. of mercury in the erect position. She was restabilized on bretylium tosylate (400 mg. three times a day), one dose producing a fall in blood pressure, with moderate postural hypotension unaccompanied by dizziness. However, when 1 gramme of chlorothiazide was taken two hours after the dose of 400 mg. of bretylium tosylate, severe postural hypotension occurred about one hour later and persisted for 30 minutes.

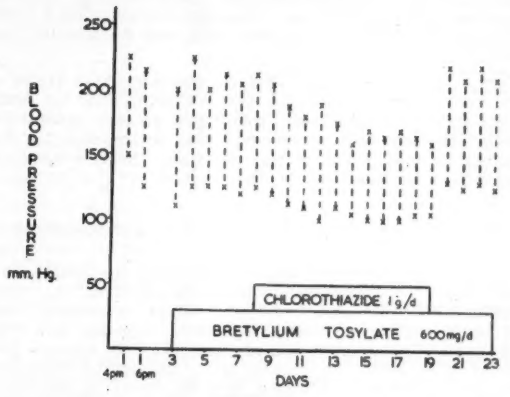

FIGURE IV.
Potentiation of hypotensive effect of bretylium tosylate by chlorothiazide.

Difficulties Experienced in Treatment.

Five patients are well stabilized on doses of 200 to 400 mg. three times a day. They feel well, and are free from side effects. Another (Case VIII) at present requires 800 mg. four times a day, together with chlorothiazide, for adequate control. On the other hand, two subjects having doses of 600 mg. four times daily have had only slight fall in blood pressure.

One difficulty is the wide variation in blood pressure from day to day, even when the dose is kept constant, and when the observations are made at the same time after the drug has been taken. This may be a manifestation of differences in the rate and degree of absorption of the drug, and it renders stabilization difficult. One patient (Case VII), who experienced severe postural hypotension on some mornings but not on others while maintained on a fixed dose of the drug, was not adequately stabilized after three weeks in hospital.

Drug tolerance (that is, the need for increasing doses in order to produce the same fall of blood pressure as is often found with ganglion-blocking agents) has also occurred in two of our 16 patients. One subject (Case X) was initially stabilized in hospital on 200 mg. of bretylium tosylate three times a day, but two weeks later twice this dosage was required. Similarly, another patient initially well controlled with 500 mg. four times a day required 800 mg. four times a day after two months' treatment.

In patients with chronic renal disease and nitrogen retention, the fall in blood pressure produced by treatment with bretylium tosylate may be associated with a rise in the blood urea level, as may be the case during treatment with ganglion-blocking drugs. In two cases the dosage of bretylium tosylate required to produce a satisfactory fall in blood pressure resulted in a rise in blood urea level which persisted until the drug was withdrawn.

CASE XII.—A male patient, aged 64 years, had been hypertensive for ten years since an attack of pyelonephritis 12 years earlier. His blood pressure was 230/130 mm. of mercury in the recumbent position, his blood urea level was 74 mg. per 100 ml., and there was an increased number of pus cells in the urine. Pyelography revealed diminished dye excretion from both kidneys, the right being more severely affected than the left. Treatment was commenced with bretylium tosylate, 200 mg. three times a day. This produced a satisfactory fall in blood pressure. The blood urea level rose slowly over the next four weeks to 180 mg. per 100 ml. When the dose of bretylium tosylate was reduced to 100 mg. three times a day, the blood urea level fell slowly.

Side Effects.

Side Effects Produced by Bretylium Tosylate.

One patient complained of nasal obstruction, which was most severe about two hours after taking 200 mg. of bretylium tosylate, but which was rapidly relieved by the inhalation of amphetamine; the same subject noticed occasional mild headaches. Another subject found that bretylium tosylate produced diarrhœa and flushing of the skin.

Three patients, all stabilized on 400 mg. three times a day, complained of pain in the region of one or both parotid glands. This pain was more or less constantly present, but was not severe, and was unaccompanied by swelling or tenderness of the parotids. In two patients the pain was localized to the region of the temporomandibular joint.

Absence of Side Effects Attributable to Parasympathetic Blockade.

Five patients who had found dryness of the mouth and constipation troublesome when being treated with mecamylamine did not experience these symptoms with bretylium tosylate, even in doses up to 3200 mg. per day. One subject who experienced blurring of vision, and another who noted unpleasant glare on moving from his office to the outdoor sunlight, as side effects of mecamylamine, were free from these troubles with bretylium tosylate.

Three men, who had become impotent when taking mecamylamine, noted restoration of potency when treated with bretylium tosylate.

Another patient, who had been treated with mecamylamine for two years, and who also had a duodenal ulcer, noted that the ulcer pain became more severe and prolonged shortly after he began treatment with bretylium tosylate, despite adherence to diet and antacids. Since dryness of the mouth and constipation, which had been troublesome while he was taking mecamylamine, disappeared with the use of bretylium tosylate, the recurrence of ulcer pain was attributed to the removal of parasympathetic blockade.

Absence of Effects on the Central Nervous System.

No patient has complained of depression or other symptoms—for example, alteration in behaviour—suggestive of central nervous effects.

Comment.

From all these observations it appears that bretylium tosylate in doses of 600 to 3200 mg. per day has few inherent side effects, and does not block parasympathetic pathways or depress the central nervous system.

EXPERIMENTAL INVESTIGATIONS.

Every person has his own particular pattern of response to autonomic stimuli (Paton, 1957). Therefore, in order to assess objectively the effects of bretylium tosylate on sympathetic and parasympathetic nervous activity in hypertensives, it was necessary to submit two groups, one hypertensive, the other normotensive, to a wide variety of tests of autonomic activity.

Material and Methods.

A group of eight hypertensive subjects were examined, together with a group of eight normotensive volunteers, both male and female, aged 20 to 40 years. These volunteers were either hospital medical officers or laboratory staff members.

Each subject, normotensive or hypertensive, was submitted to the following series of nine tests of autonomic activity, on at least three separate occasions after mecamylamine or bretylium tosylate or a placebo tablet had been given.

Normotensives were tested three to four hours after taking one dose of the drug concerned (5 mg. of mecamylamine or 200 mg. of bretylium tosylate), the nature of which was unknown to them. However, hypertensives were tested when they had been taking either mecamylamine or bretylium tosylate, or sedatives only, for several days. Tests were made when the diastolic blood pressure, measured in the erect posture, had been reduced to 100 mm. of mercury by either mecamylamine or bretylium tosylate (three to four hours after ingestion of the morning tablet). In some cases the nature of the drug was unknown; but those subjects who had in the past been treated with other hypotensive agents were aware that a drug new to them was being taken.

Tests Depending on Reflex Sympathetic Nervous Activity.

These tests consisted of examining the pupil for dilatation after pinching the skin of the neck, and in measuring the effect of exercise and erect posture on pulse rate and on blood pressure.

Tests Depending on Parasympathetic Nervous Activity.

These tests consisted of examining pupillary reactions to light and convergence, of measuring accommodation for near vision, and of measuring the effect of carotid sinus pressure and eyeball pressure on pulse rate and blood pressure. In addition a study of reflex salivation was made as follows:

Saliva secreted by each subject was collected by means of a saliva evacuator into a graduated test tube for each of two periods of 10 minutes. During the first period 0·1 ml. of normal saline was dropped on the tongue every two minutes, and during the second period 0·1 ml. of fresh lemon juice was dropped on the tongue every two minutes.

Results.

In both groups the response to autonomic stimuli varied greatly from person to person under control conditions. It was therefore difficult to draw firm conclusions from findings in one test; however, considering the tests as a whole, it was clear that in the hypertensive group both drugs produced marked diminution of ocular and circulatory reflex sympathetic activity, whereas bretylium tosylate, unlike mecamylamine, did not inhibit parasympathetic reflex activity (Table I). Complete absence of parasympathetic blocking action by bretylium tosylate was strikingly demonstrated in salivation studies on hypertensives. With bretylium tosylate the resting salivary secretion was the same as when no drug was taken, and the reflex response was the same, whereas with mecamylamine the resting salivary secretion was always greatly diminished and there was a diminished response to stimulation with lemon juice (Figure IV).

These findings indicate that in hypertensive subjects bretylium tosylate in effective therapeutic dosage has no parasympathetic blocking activity.

In normotensive volunteers the differences observed were not so consistent. There was only slight inhibition of sympathetic activity by both drugs, and there was some inhibition of parasympathetic activity by mecamylamine, but not by bretylium tosylate.

These findings were almost certainly related to the fact that a single dose of either drug, in particular a dose of 200 mg. of bretylium tosylate, is insufficient to produce sympathetic block in many normotensive individuals; but in two individuals in whom bretylium tosylate produced manifestations of sympathetic block there was no diminution of parasympathetic activity.

Salivation studies were not as conclusive in normotensives, for similar reasons, and also because of the great

variation in the range of salivary secretion under control conditions from day to day.

Animal Investigations.

Effect of a Large Rapid Intravenous Dose of Bretylium Tosylate.

In the dog under "Nembutal" anæsthesia, the injection of bretylium tosylate (10 mg. of base per kilogram) is followed by a slight decrease in pulse rate, and a sudden fall in blood pressure which reaches its minimal value in about 15 seconds. The pressure then rises, reaching the original level after another 15 seconds. The rise in pressure continues slowly, reaching a maximum after about 10 minutes, then slowly falls again to its original level.

TABLE I.

Summary of Effects of Bretylium Tosylate on Sympathetic and Parasympathetic Reflex Activity in Eight Hypertensive Subjects.

Substance Tested.	Effect on Sympathetic or Parasympathetic Nervous System.	Reflex Tested.		
		Circulatory.	Ocular.	Salivatory.
Mecamylamine	Sympathetic inhibited.	8	6	—
	Parasympathetic inhibited	4	6	8
Bretylium tosylate.	Sympathetic inhibited	8	6	—
	Parasympathetic inhibited	0	0	0

Tests of Reactivity to Pressor Amines.

Several pressor substances were tested before and after an intravenous injection of bretylium tosylate. The pressor effects of noradrenaline, adrenaline, "45/50" (Burroughs Wellcome), ephedrine and mephentermine were all increased after treatment with bretylium tosylate (Table II).

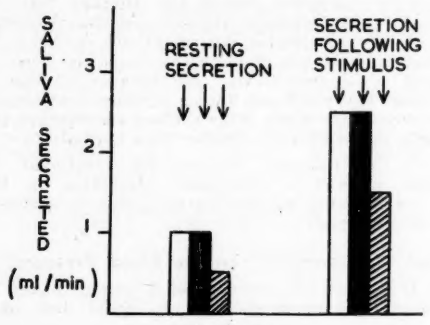

FIGURE V.

Comparison of effects of mecamylamine and bretylium tosylate on salivary secretion in a hypertensive subject. Open columns, controls; solid columns, bretylium tosylate; hatched columns, mecamylamine.

DISCUSSION.

The problems raised by the advent of any new drug are many. At a clinical level, information is needed on the action of the drug, on what doses are required, on what short-term and long-term toxic effects are produced, and finally on what is the likely place of the drug in therapeutics.

In a restricted short-term clinical study it may not be possible to provide definite answers to these questions, although it is possible to provide information, the value of which is affected by the bias introduced when a small sample of a population is studied. In an attempt to overcome this objection three main groups of patients have been studied—namely, those who have responded inadequately and have experienced severe side effects when treated with ganglion-blocking agents, those who have responded well to treatment with these drugs, and some subjects who have had no previous treatment for hypertension.

From experience with such patients, it is apparent that bretylium tosylate lowers the blood pressure of hypertensive subjects, but some require very large doses—for example, three grammes a day before any effect is apparent. Such patients, who may well comprise a significant proportion of hypertensive patients, are almost certainly not suitable for treatment with bretylium tosylate.

TABLE II.

Effect of Various Pressor Amines on Femoral Artery Peak Systolic Pressure in a Dog under "Nembutal" Anæsthesia Before and After Bretylium Tosylate.

Drug.	Change in Systolic Blood Pressure in Femoral Artery. (Millimetres of Mercury.)	
	Before Bretylium Tosylate.	After an Intravenous Dose of 5 mg. of Bretylium Tosylate Base per Kilogram.
Nor-adrenaline (1 µg. per kilogram) ..	+35	+102
Adrenaline (1 µg. per kilogram)	+15	+35
Mephentermine (10 µg. per kilogram) ..	0	+24
Ephedrine (100 µg. per kilogram) ..	0	+14
45/50 (1 mg. per kilogram)	+24	+38

Subjects who exhibit unpredictable and erratic responses—for example, a satisfactory fall of blood pressure on one day, a slight fall only on the next, and then severe postural hypotension on another occasion—are found, and are also not suitable for treatment with the drug. This uneven response may be in part caused by irregular absorption from the bowel.

Patients with chronic renal disease and nitrogen retention must be treated with great caution, since a fall in systemic blood pressure may be followed by renal failure. The dosage of bretylium tosylate in these cases will be governed by the blood urea level.

There remains a group of persons—about one-third of this small series—who are well stabilized on moderate doses of bretylium tosylate (up to 600 mg. four times a day), feel well—better than they did on ganglion-blocking agents—and have no side effects referable to parasympathetic blockade. This group is eminently suitable for treatment with bretylium tosylate; but we have as yet no means of determining in advance whether a patient will fall into this group. Probably, at present, the drug should be tried on those who have experienced severe side effects on ganglion-blocking agents, or who have been difficult to stabilize on these drugs.

The selective action of bretylium tosylate on adrenergic nerves is undoubtedly its one great advantage over ganglion-blocking agents. We have observed no central depressor or parasympathetic blocking activity at all in any subject; absence of parasympathetic blockade has been confirmed experimentally. We have not seen any serious side effects of any other nature.

There is much to be learnt about the mode of action of this drug, the elucidation of which will be hastened when a quantitative method of estimation in body fluids is found. There is no evidence that the hypotensive action of bretylium tosylate is mediated by depletion of noradrenaline stores in the vessel wall, as occurs with reserpine. It is of interest that, while the drug inhibits sympathetic transmission, it renders the arteriolar wall more sensitive to the action of pressor amines—for example, adrenaline and noradrenaline. This phenomenon, also found after sympathectomy, is of clinical significance.

It suggests that bretylium tosylate will produce a rise in blood pressure if it is given to a subject with hypertension produced by increased levels of circulating pressor amines, as in the case of phæochromocytoma; but we have as yet not had the opportunity to test the drug as a provocative agent in this condition.

Further studies of the action of the drug should lead to an increased knowledge of the neuro-humoral control of vascular resistance in the normal and hypertensive person.

SUMMARY.

1. A small clinical study has been made of the action of bretylium tosylate ("Darenthin", Burroughs Wellcome), a hypotensive agent which selectively blocks adrenergic nerves. Approximately half the patients studied had been difficult to treat previously with ganglion-blocking agents.

2. The oral dose required to lower the blood pressure of a hypertensive patient varies from 100 to at least 800 mg. An effective single dose produces a fall in systolic and diastolic pressures for about five hours. There is usually only a slight fall in blood pressure in recumbency, but a marked fall occurs in the erect posture.

3. The action of the drug is potentiated by chlorothiazide.

4. No serious side effects were observed. The drug has no parasympathetic blocking activity.

5. One third of the patients studied have responded well to treatment with the drug. However, some subjects are very difficult to stabilize with the drug. These, and others who develop tolerance and require increasing doses, are not suitable for treatment.

6. The use of bretylium tosylate in patients with chronic renal disease and nitrogen retention may be followed by a rise in the blood urea level.

7. The place of the drug in the treatment of hypertension, and its mode of action, are discussed.

ACKNOWLEDGEMENTS.

We are grateful to Dr. K. Severin Alstad, of Burroughs Wellcome (Australia) Ltd., for generous supplies of bretylium tosylate ("Darenthin", Burroughs Wellcome), and to Miss P. Walsh and Miss V. Hansen for technical assistance.

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OBSERVATIONS OF THE USE OF "DARENTHIN", A NEW GANGLION-BLOCKING AGENT.

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BOURA, COPP AND GREEN in 1959 found that benzyl quaternary ammonium compounds had a ganglion-blocking effect which was predominantly on the peripheral sympathetic nervous system, and described the compound bretylium tosylate, whose formula is shown in Figure I. This substance has a hypotensive effect in man and has been called "Darenthin".

Preliminary clinical trials on hypertensive patients at University College Hospital, London, were encouraging, especially in view of the absence of severe side effects, at the time when a limited supply of the drug was made available to us for trial.

Patients Studied and Methods.

Nine patients admitted to Royal Prince Alfred Hospital for control of systemic arterial hypertension were found suitable for study; two were males and seven females, their ages ranging from 40 to 55 years (Table I). Three were suffering from frank malignant hypertension, and the remaining six had diastolic blood pressures rarely below 115 mm. of mercury prior to therapy; of these six, four had at least Grade II retinopathy, and two could not be assessed in this regard because of long-standing bilateral primary ocular disorders, glaucoma in one case and corneal opacities in the other.

TABLE I.

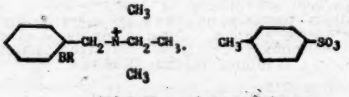
Case Number.	Sex.	Age. (Years.)	Highest Blood Pressure Before Treatment. (Mm. of Mercury.)	Lowest Blood Pressure Before Treatment. (Mm. of Mercury.)	Grade of Retinopathy.	Blood Urea Level on Admission. (Mg. per 100 ml.)
I	F.	52	220/130	195/110	II	21
II	F.	56	250/140	200/120	II	35
III	F.	41	250/140	220/140	IV	51
IV	F.	52	240/140	180/110	—	29
V	F.	37	230/140	190/120	II	32
VI	F.	53	235/145	210/140	II	39
VII	M.	44	205/125	190/115	—	37
VIII	M.	51	250/160	240/130	IV	90
IX	F.	48	300/180	240/150	IV	36

Routine investigations included a full blood count and estimation of the erythrocyte sedimentation rate and blood urea content, an X-ray examination of the chest, electrocardiography, a microscopic examination of urine, urinary catecholamine estimation, a urine concentration test and intravenous pyelography. These investigations, and a series of observations of the blood pressure variations in hospital, were completed before any therapy was commenced. All nine patients showed electrocardiographic evidence of left ventricular preponderance, although not all had clinical evidence of increased heart size; two had an elevated blood urea level, and because of this one patient (Case VIII) did not have a pyelographic examination; however, plain X-ray films showed his kidneys to be of equal size and somewhat smaller than normal.

None of the patients selected for treatment with "Darenthin" showed a significant alteration in blood pressure over a week of observation prior to commencement of drug therapy.

Effect of "Darenthin" on the Blood Pressure.

Figure II depicts the response of a patient (Case III) with malignant hypertension to an initial dose of 400



373.C.57 p-toluene sulphonate

FIGURE I.
Formula of "Darenthin".

mg. of "Darenthin". There was an obvious hypotensive effect, much more marked in the upright position, maximal six to seventeen hours after administration of the drug; and 48 hours after this excessive test dose, the blood pressure was still not quite back to its original level. The effect of single test doses became apparent as early as one hour after their administration, the lowest blood pressure readings were delayed as long as 17 hours, but were usually recorded between three and eight hours after the

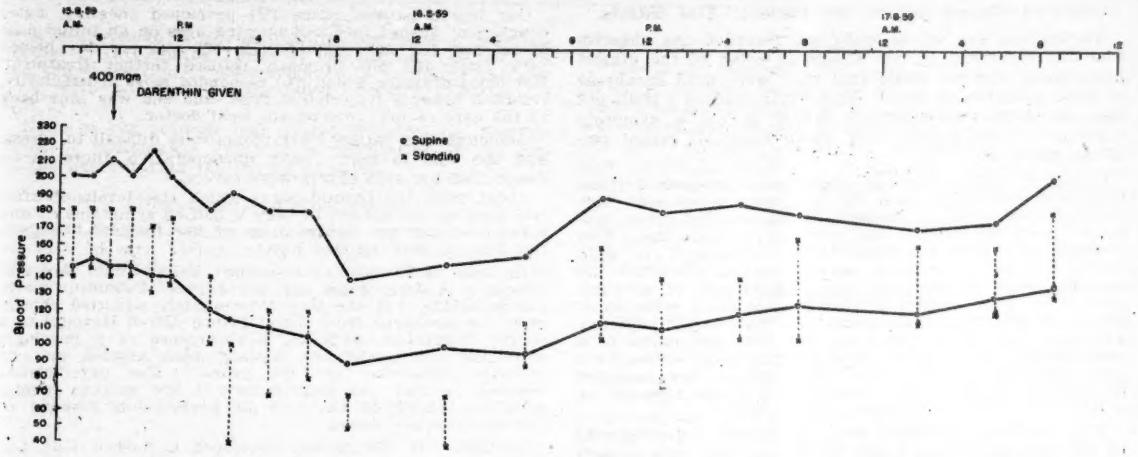


FIGURE II.

The effect of a single dose of 400 mg. of "Darenthin" on the blood pressures (standing and supine positions) in Case III.

dose had been given, and the blood pressure took up to 48 hours to return to its original level. On the other hand, one patient (Case I) showed no response at all to a 200 mg. test dose, but when given 200 mg. at eight-hourly intervals, developed marked postural hypotension and severe anginal pain after 48 hours, necessitating withdrawal of the drug. Such a cumulative effect is to be expected from a drug whose duration of action is long, and this has important implications during the period of stabilization.

Seven of the nine patients were eventually stabilized on "Darenthin", and the range of dosage varied widely.

One patient (Case III) was discharged from hospital, well controlled, on 300 mg. per day, with chlorothiazide supplement.

Another (Case V) required 2800 mg. per day in hospital, and during follow-up investigation in the out-patient department this dose was increased to 3400 mg. per day, with no effect on the blood pressure, which had returned to its original level of 220/145 mm. of mercury. Crushing the "Darenthin" tablets made no difference; prior to this patient's admission to hospital she had already been given mecamylamine, which produced intolerable side effects, chlorothiazide, which produced severe diarrhœa, and reserpine, which induced a severe, though temporary, depressive episode.

Effect of "Darenthin" plus Chlorothiazide.

Three patients received supplementary chlorothiazide, and in each case we observed a very definite drop in both systolic and diastolic blood pressures, which we attribute to this drug.

Figure III illustrates the response of one patient (Case IX) with malignant hypertension. It may be seen that her blood pressure was reduced to a fairly steady level of about 200/130 mm. of mercury on 600 mg. of "Darenthin" per day; but the introduction of chlorothiazide, 1 gramme per day, resulted in a drop to uncomfortable levels over a period of several days; cessation of chlorothiazide was followed by a steady rise of blood pressure, while its reintroduction one week later resulted in a fall to fairly satisfactory levels. Figure IV shows in more detail the blood pressure response of the same patient to the reintroduction of chlorothiazide; the first day shown was prior to therapy, and on the second day the patient was receiving "Darenthin" alone. Five days later, after four days of combined therapy, we were satisfied that we appeared to have an ideal combination for this patient, whose blood pressure, on her admission to hospital, was 300/170 mm. of mercury.

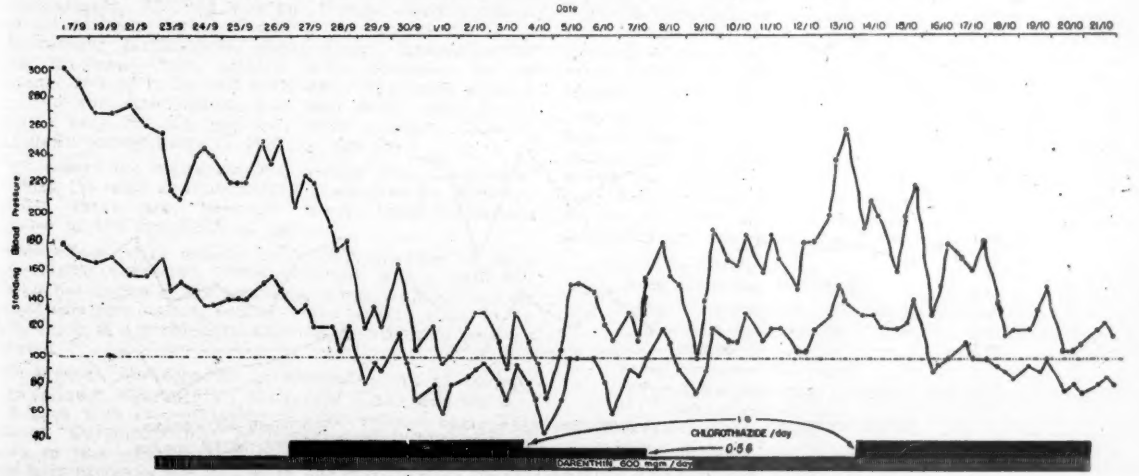


FIGURE III.

Complete record of blood pressure (standing) in Case IX, during patient's stay in hospital.

Effect of "Darenthin" on the Patient: Side Effects.

Throughout the whole study we regarded the observation and recording of side effects as being of the utmost importance, and we found that they were mild or absent in seven of our nine cases. Under this heading I shall not discuss postural hypotension, which is not a symptom *peculiar to "Darenthin", and which beset all except two* of our patients.

Our first patient suffered slight nasal congestion when treatment was begun with 200 mg. three times each day, which proved to be an excessive dose; however, when sent home taking 300 mg. per day, she was symptom-free. This woman, who had previously been accustomed to mild angina of effort, suffered severe angina whenever the standing blood pressure fell below 120/80 mm. of mercury, so that we were obliged to stabilize her blood pressure at about 140/90 mm. of mercury; this was easily achieved. After two months of treatment, she first complained of a symmetrical pain in each parotid region when eating; the pain was sharp and lasted for only a few minutes immediately after the first mouthful, but was followed by a mild and persistent soreness to palpation.

This identical symptom was volunteered independently by five patients (Cases I, III, V, VII and IX), and in each case the onset was after two or more months of therapy. The pain was often brought on by the sight of food, and could be elicited by dropping lemon juice onto the patient's tongue; it appeared to be independent of the act of swallowing.

The patient in Case II was subjected to rapid dosage changes from an initial 300 mg. to 900 mg. per day, with accompanying severe nasal congestion. Soon after, the dose was raised to 1200 mg. per day, with an excellent blood pressure response; but so severe were the nasal obstruction and superadded bronchospasm that we were obliged to withdraw the drug. Cessation of therapy resulted in the disappearance of symptoms over a period of three days.

It is possible that the distressing side effects which occurred could have been avoided by more gradual increment of dosage and, perhaps, by the addition of chlorothiazide.

Our third patient (Case III) complained of very slight nasal congestion with facial flushing on a dose of 400 mg. per day; but when she was discharged from hospital taking 300 mg. per day *plus* supplementary chlorothiazide, she had no symptoms at all. After the commencement of therapy her severe headaches disappeared and the retinopathy diminished greatly, although the original blood urea level of 51 mg. per 100 ml. rose to 100 mg. per 100 ml.

Our fourth patient (Case IV) developed sneezing, nasal congestion, flushed face and burning eyes on an initial dose of 600 mg. per day; reduction to 400 mg. per day helped very little, and she promptly refused further treatment. Her blood pressure, which had responded most satisfactorily, returned towards its original level, and she was sent back to the care of her unfortunate local doctor.

Although this patient's symptoms were difficult to assess, and she was in many ways uncooperative, there is no doubt that her side effects were severe.

Apart from the parotid pains which she developed after two months, the patient in Case V had no symptoms at any stage of either her hypertension or her treatment, despite the dose of 3400 mg. per day.

In Case VI the patient responded well, without any side effects, to a dose of 600 mg. per day of "Darenthin" with chlorothiazide; but she was unfortunately admitted shortly after her discharge from Royal Prince Alfred Hospital to a nearby institution, suffering a recurrence of a psychotic state for which she had already been treated on two separate occasions over the years. Her psychiatrists assured us that our contribution to her present mental state was negligible, but they did nevertheless suspend all anti-hypertensive drugs.

In Case VII the patient developed a flushed face and stuffy nose on a dose of 400 mg. per day; but when he was discharged from hospital some weeks later, taking 1200 mg. per day, he was completely free of symptoms. When he was last examined, his blood pressure was well controlled, he felt well and his blood urea level was 44 mg. per 100 ml. His freedom from side effects we attribute to gentle dosage increments.

In one of our more severe cases (Case VIII) the patient already had a blood urea level of 90 mg. per 100 ml. on his admission to hospital, had had a recent minor cerebral vascular accident and was found to have grade IV retinopathy; he was apparently well controlled on 500 mg. per day of "Darenthin" *plus* reserpine, with no alteration in the blood urea level. He had no side effects, and on his discharge from hospital no longer had papilœdema. Although the blood pressure was kept under moderately good control, he remained weak, listless and mildly anæmic until two months later, when he died rapidly in his district hospital in uræmic coma.

In Case IX the patient, also with malignant hypertension, complained of mild snuffles, tight temples, flushed hot face and sore eyes from an initial 600 mg. per day of "Darenthin", but some weeks later, when she was discharged from hospital taking the same dose, *plus* chlorothiazide, she was symptom-free. Subsequently she, too, developed the pain in the parotid region already described. This patient's visual acuity improved remarkably during her stay in hospital, and papilœdema subsided in three weeks; her blood

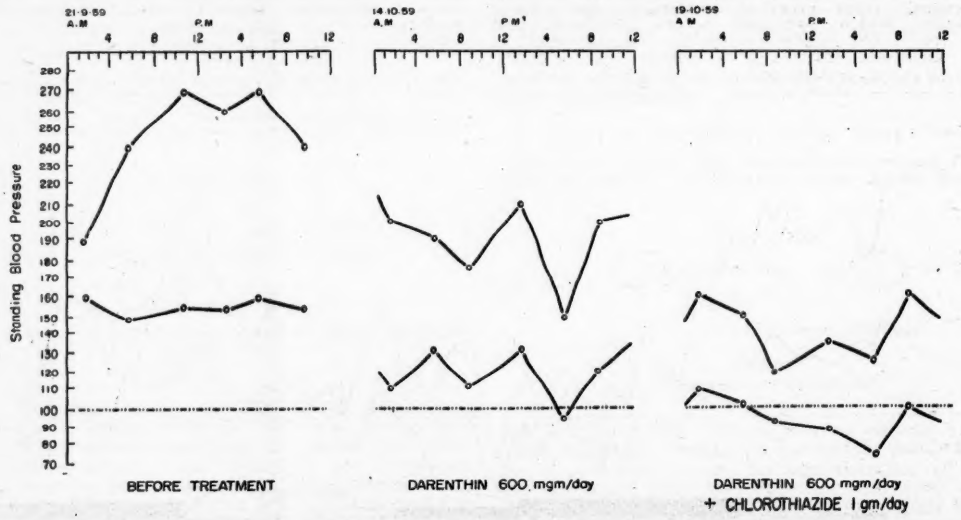


FIGURE IV.

Record of blood pressure (standing) in Case IX on three separate days, to show the effect of combined therapy.

urea level rose to 56 mg. per 100 ml., but has not risen any further in two months. Prior to her admission to our unit she had had a trial of mecamylamine in maximum tolerated dose, with no effect on the blood pressure (Figures III and IV).

None of our patients had electrocardiographic improvement or radiological evidence of diminution in the size of the heart during the period of study.

Discussion and Conclusions.

One of the problems we encountered was that of spacing of doses in each 24-hour period. When "Darenthin" was given in eight-hourly, equal doses, the effect was often of the type seen in Figure V, the blood pressure being too

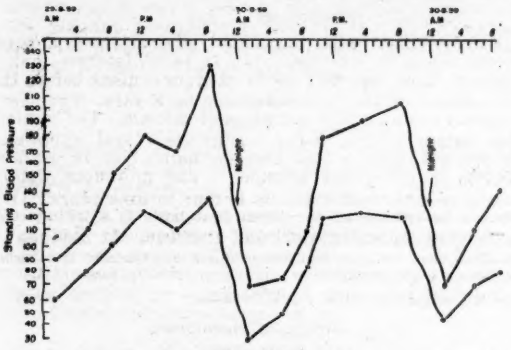


FIGURE V.

Blood pressure (standing) in case III, on a dosage of 100 mg. of "Darenthin" at intervals of eight hours, 6 a.m., 2 p.m. and 10 p.m.

high during the afternoon and evening, but much too low during the morning. After trial and error, we concluded that the most reliable way of producing a satisfactory even response was to give the drug only twice each day, at 6 a.m. and 2 p.m., the earlier dose being the larger; we also thought that chlorothiazide, quite apart from its hypotensive action, did help to flatten out the "afternoon hump". Even so, two patients (Cases III and IX) still noticed that they had a tendency towards postural hypotension each morning for an hour or two after rising.

In general, we found "Darenthin" to be a satisfactory agent for the reduction of blood pressure in hypertensive patients, especially when used in combination with chlorothiazide. Control was not always easily attained, and all patients were in hospital for several weeks for this reason; furthermore, slight dosage increases after their discharge from hospital were necessary for all patients deemed to be well controlled. The range of doses required for stabilization was very wide, one patient needing only 300 mg. per day, while another (Case V) was quite unresponsive to 3400 mg. per day.

We regard the indications for therapy with "Darenthin" as being the same as those currently accepted for mecamylamine; there are, however, fewer contraindications because of the specificity of action.

Side effects were usually mild, and tolerance to them undoubtedly developed. The exception was a pain felt behind the angles of the mandible, worse with eating; we regard this pain as originating in the parotid gland or its duct, but it is a problem to which more attention must be directed.

At present, our schedule at commencement of therapy is as follows: "Darenthin", 200 mg. at 6 a.m. and 100 mg. at 2 p.m., with chlorothiazide, 500 mg. twice a day. The dose of "Darenthin" may be increased at intervals of 48 hours in increments of 100 mg. per day until the daily dose is in excess of 800 mg., when one may be more liberal with the rate of increase. The dose of chlorothiazide is left constant, and it is our custom to supply extra potassium.

Summary.

"Darenthin" satisfactorily reduced the blood pressure in eight of nine patients admitted to hospital for the control of systemic arterial hypertension. In seven cases side effects were absent or very mild, while in the other two their severity necessitated withdrawal of the drug. The maximum effect of a single dose occurred at times varying from three to seventeen hours after its administration, and the duration of action was as long as 48 hours. Chlorothiazide markedly augmented the effect of "Darenthin" in the three cases in which this combination was used.

Acknowledgements.

I am indebted to Dr. K. S. Alstad, Medical Director of Burroughs Wellcome and Co. (Australia) Ltd., for the supply of "Darenthin" for trial, and to Professor C. R. B. Blackburn for his help and advice. My thanks are also due to Mr. Woodward-Smith, Department of Illustration, University of Sydney, for the graphs.

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OSTEOPOROSIS.[1]

By A. I. RHYDDERCH, F.R.C.S., F.R.A.C.S.,
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OSTEOPOROSIS, probably better defined as hypo-opacity of bone to X rays, is a common finding in orthopædic conditions. It immediately provokes the challenge to determine its cause.

Localized Hypo-opacity.

The causes of localized hypo-opacity are well known and often obvious. I would instance the following: (i) infection, (ii) neoplasm, (iii) immobilization, (iv) reflex dystrophy in the limbs.

Common specific examples seen in practice are as follows: (i) hypo-opacity of the phalanges of the finger in relation to overlying septic infection, (ii) the spotty decalcification of Sudek's atrophy, (iii) the hypo-opacity of the limb following immobilization.

The development of hypo-opacity on a previously normal bone is dependent upon an intact blood supply. Avascular necrosis of the head of the femur, scaphoid and talus is made evident by the density of the affected part, contrasted with the surrounding disuse atrophy.

In discussing the generalized forms of osteoporosis, I should like to quote Dr. Edward Reifenstein's suggested classification of metabolic bone disorders. It succinctly shows the possible variants of all metabolic disease of bone with his conception of a normal calcified bone mass. At any one time this is the balance between the constant deposition and resorption of a living vital tissue.

Too little calcified bone
- Bone formation too little
  - Too little formation of matrix: Osteoporosis
  - Too little calcification of matrix: Osteomalacia or rickets
- Bone resorption too much
  - Too much resorption of matrix and calcium: Osteitis fibrosa generalisata

Too much calcified bone
- Bone formation too much
  - Too much formation of matrix: Hyperosteogenesis
  - Too much calcification of matrix: Non-existent

[1] Read at a meeting of the New South Wales Branch of the British Medical Association on May 28, 1959.

Bone resorption too little
Too little resorption of matrix and calcium: Osteosclerosis

We are not concerned tonight with the problem of too much calcified bone.

The following provisional classification of the causes of osteomalacia or rickets is adapted from Dr. E. C. Reifenstein:

Insufficient absorption
Low calcium absorption
Low calcium diet
Gastro-intestinal disease
Hypothyroidism?
Low vitamin D absorption
Low vitamin D diet (avitaminosis D)
Gastro-intestinal disease
Hyperthyroidism?
Vitamin D resistant rickets
Excessive excretion of calcium
Loss from kidney
Calcium as a base in acidosis
Pyelonephritis with distal tubular damage
Fanconi syndrome with proximal tubular damage
Low renal threshold
Idiopathic hypercalcuria?
Renal infection?
Hyperthyroidism?
Loss from placenta
Frequent pregnancy
Loss from breast
Prolonged lactation
Excessive utilization of calcium
Bone formation too great
Healing osteitis fibrosa generalisata
Insufficient mobilisation of calcium
Bone resorption too little
Osteoporosis with insufficient calcium intake.

Dr. Reifenstein's provisional classification of the causes of osteitis fibrosa generalisata may be summarized as follows:

Excessive parathyroid hormone
Primary hyperparathyroidism
Secondary hyperparathyroidism
Excessive acids in body fluids (chronic systemic acidosis)
Renal acidosis with decreased glomerular function: renal osteitis fibrosa generalisata ("renal rickets")
Renal acidosis with normal glomerular function
Excessive rate of cellular metabolism
Hyperthyroidism
Excessive osteoclastic activity
Poisoning with chemicals

When osteoporosis, or the specific bone disorder in which there is too little calcified bone due to insufficient formation of matrix, was suggested as a topic for discussion, it was primarily brought forward to air current views on the ætiology and treatment of senile and post-menopausal osteoporosis. Most of this paper will be confined to a discussion of these two entities.

For completeness, Dr. Reifenstein's provisional classification of causes of osteoporosis is presented in summarized form:

Defect in osteoblasts
Loss of stress and strain
Atrophy (osteoporosis) of disuse
Deficient œstrogen
Post-menopausal state
Pre-menopausal ovarian insufficiency
Congenital osteoplastic defect
Osteogenesis imperfecta
Defect in matrix
Deficient androgen
Senile state in males
Presenile testicular insufficiency
Deficient protein
Malnutrition
Avitaminosis C (scurvy)
Hyperthyroidism
Diabetes mellitus
Cushing's syndrome
Chronic corticoid therapy
Prolonged stress
Defect unknown
Acromegaly
Idiopathic osteoporosis

Before I deal with the actual clinical pattern, several points must be stressed. (i) It is of interest that the skeleton must lose 30% of its calcium content before there are changes in the bone detectable by X rays. The average skeleton contains 1150 grammes of calcium. The minimum loss before present X-ray techniques reveal hypo-opacity is 345 grammes. The average daily loss in metabolic studies is 0·1 to 0·2 gramme. The minimum time for loss detectable radiologically is four to nine years. (ii) It cannot be reiterated too often that bone is a living tissue, being constantly deposited and absorbed. At any one time the amount of calcified bone mass represents the balance between bone deposition and bone resorption. (iii) Hormones influence this equilibrium.

Anabolic Hormones.

Repeated metabolic studies have shown that the œstrogenic and androgenic hormones produced by the gonads and adrenal cortex stimulate the anabolism of protein and osseous tissues. Œstrogen induces maximal calcium retention. The combination of both androgen and œstrogen does not cause greater nitrogen retention, but results in considerably greater calcium retention than the œstrogen or androgen alone. "Androgen and œstrogen have qualitatively similar but quantitatively different effects upon protein and osseous tissues."

It is of interest that in pigeons serum calcium levels up to four times normal are found just before ovulation. This rise has been proved to be due to œstrogen stimulation and not connected with the parathyroid.

The Anti-Anabolic Steroid Hormones.

The anterior pituitary adrenocorticotrophic hormone (ACTH) and the adrenal cortical steroids (hydrocortisone, cortisone and related compounds) produce protein depletion and osteoporosis. One of the prime features of Cushing's syndrome is osteoporosis. Excess cortisone administration gives rise to the same features.

Reifenstein and others have surveyed the literature and found 38 cases of spontaneous fracture ascribed to the effects of cortisone. Fractures occurred within periods varying from one month up to three years, with an average of 15 months, and after the administration of 37 grammes.

The knowledge of the action of these hormones, together with metabolic and urinary steroid estimations, sheds light upon the development of senile and post-menopausal osteoporosis.

With advancing years the anabolic influences lessen, abruptly in the female at the menopause, and gradually in the male. The resorption of bone continues undiminished, due to the continuing action of the anti-anabolic steroid hormones, before symptoms arise. These changes progress silently over a period of years.

Symptomatology.

Females greatly outnumber males. There are two common modes of onset, as follows. There may be the sudden development of acute pain in the back, with or without girdle pain, almost always due to a spontaneous compression fracture. On the other hand, the condition

may come on chronically, with gradually increasing deformity of the thoracic and lumbar segments of the spine with or without backache.

The X-ray appearances of the spine are characteristic—almost translucent vertebræ, often only the upper and lower plates being visible. The bodies are commonly fish-tail, wedged or compressed. The intervertebral disc is grossly expanded. Numerous fractures may be visible. The distribution of these changes is maximal in the vertebral column and pelvis; there is little change in the extremities or skull.

The differential diagnosis is from osteomalacia, osteitis fibrosa and generalized myelomatosis and carcinomatosis.

The distribution of the lesions, the presence of cysts or pseudo-fractures, serum calcium and phosphate levels, the serum alkaline phosphatase content, the electrophoretic pattern, the presence of a primary tumour, sternal marrow tests, etc., all help in the diagnosis.

Treatment.

Bracing.

The immediate treatment is support to the spine by the application of a light spinal brace to prevent further deformity or fracture.

Occasionally, in the acute types, because of the severity of the pain, recumbency may be necessary for a very limited period. Prolonged bed rest is detrimental, both on general grounds in the elderly, and specifically as a cause of disuse atrophy by withdrawal of the normal stress and strain stimulus to osteoplastic activity.

Hormonal Therapy.

Hormones (methyl testosterone and stilbœstrol) should be given by mouth, together with adequate calcium and vitamin D. In the light of the metabolic studies previously mentioned, hormones should be given for years. Maximal recalcification cannot be expected before then.

More recently, intramuscular depot preparations have been developed by the Squibb Laboratories, which are effective for one month. "Deladumone", in a dosage of 1 to 2 ml. given once a month, has been proven effective in reversing the negative calcium balance. As yet this drug is not available in Australia.

So far I have given patients these hormones only for a limited period, as a rule for only a few months after their pain has been controlled. My reason has been that I am not aware of the late results of hormonal dosage of that order extending over years. Probably it is harmless, as similar dosages have been used to control prostatic and mammary cancer over longer periods.

The combination of androgen and œstrogen has been found to give maximal effect with minimal undesirable side-reactions.

No patients so far treated have achieved any return to normal architecture, though their symptoms have been in the main completely relieved.

Reports of Cases.

The following are typical cases encountered in practice.

Senile Osteoporosis.

The patient was a man, aged 78 years. I operated upon him for a trochanteric fracture of the femur in 1954. At that time he had no symptoms referable to his spine. In 1956 he bent over in the bath to pick up a piece of soap, when he heard something crack in his back and was seized with violent pain. The pain was so severe that I was called to see him at home. X-ray examination revealed multiple pathological compression fractures of the dorso-lumbar region. Treatment was by the application of a spinal support, and the administration of hormones, multivitamin preparations and calcium. Today he is still at work in the city. In the week-ends he gardens and clips his own edges.

Post-Menopausal Osteoporosis.

A female patient, aged 62 years, was first examined in the out-patient department, complaining of chronic back pain of some years' duration. The X-ray findings were characteristic. Gross thoracic kyphosis was present. Only partial relief was obtained from a spinal support, mainly because of the gross mechanical deformity. This patient developed vaginal hæmorrhage.

A second patient was examined in January, 1958, having suffered the gradual onset of severe back pain over nine months, maximal in the thoracic segment of the spine. X-ray examination revealed compression fractures of the ninth, tenth and eleventh dorsal vertebræ, with widespread changes of osteoporosis. She was treated by the application of a Taylor brace and the administration of hormones, with complete relief of pain.

Comment.

At the present time most of the patients treated are pain-free. In the light of facts revealed during the preparation of this paper, I believe that they should again have hormonal therapy to forestall any relapse.

Prophylaxis.

Reifenstein points out that there is a strong case for the routine administration of anabolic steroid hormones to the elderly and to the post-menopausal female.

Only a small percentage of patients will develop frank symptoms of osteoporosis — pain, deformity, etc.; but the other manifestations — decreased muscle mass and ready fatigability — are inevitable and reflect decreasing anabolic activity. That these changes can be influenced — slowed down, if not reversed — may yet result in the routine prophylactic taking of hormones as one of the elixirs of life. Man is not prepared to accept the inevitable.

Acknowledgement.

I am indebted to papers written by Dr. E. C. Reifenstein on clinical orthopædics for the results of metabolic studies and for his classification.

OSTEOPOROSIS.[1]

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I THINK Dr. Freddy Homburger, the American, puts it rather well when he writes:

> Osteoporosis is a chronic disease that passes unrecognized more often than most other chronic diseases, has caused more pain than many of them and yet is more amenable than any other to simple therapeutic measures. It probably holds a record among chronic diseases for having led to false diagnosis.

Usually the early complaint is pain in the back associated with weakness, and this line-up of symptoms very often leads to a diagnosis of "rheumatism". For this reason, it is necessary for the general practitioner to be aware of the clinical manifestations of osteoporosis, and of the various diseases of the symptom complex of which it forms part.

Osteoporosis is still much overlooked and neglected, in spite of the prevailing knowledge that it is a relatively common condition occurring in post-menopausal women and not at all rare in men. More regrettable is the fact that, when the condition is diagnosed, it is frequently passed off as an inevitable and irreversible condition of senescence.

It will be useful to discuss the normal physiology of bone. The osseous mass is a living tissue that is constantly fluctuating as it undergoes growth, resorption and remodelling. It consists of specialized connective tissue in which the intercellular substance is impregnated with mineral salts. This is the bone matrix or osteoid, and has as its major component a protein polypeptide. The mineral salts

[1] Read at a meeting of the New South Wales Branch of the British Medical Association on May 28, 1959.

are mostly calcium carbonates and phosphates serving as a lattice on which is deposited a mantle of adventitious organic substances. Specialized cells, the osteoblasts and osteoclasts, are concerned with bone production and resorption respectively. The mineral composition of bone varies in different persons of the same age and sex, and also in the same bone, at different times; this is because it reflects the qualitative and quantitative changes in the biological fluid surrounding the bone. There is still a difference of opinion concerning the physical relationship of bone matrix to salts. Either the protein-carbohydrate moieties combine with the minerals to form an indissociable complex, or the bone matrix merely provides a structure on which the crystals build. Much of the sequential pattern of the formation and absorption of bone is still conjectural, and the interplay of hormones and of nutritive agents also awaits further research.

The fundamental disturbance in osteoporosis is defective osteogenesis due to faulty matrix formation, and is therefore a disease of protein metabolism. It is characterized by a reduction in the number and size of trabeculæ, as well as by a thinning of the cortex. It must not be confused with osteomalacia and osteitis fibrosa, in which also there is insufficient calcified bone, owing to increased bone resorption. These three conditions all show decreased density of bone radiologically. This shows in the film only when 30% demineralization has occurred, and therefore can be of no help in early diagnosis of these diseases. Serum calcium and phosphorus values are generally normal in osteoporosis.

Hypercalciuria when present occurs only with rapidly developing osteoporosis, in which osteolysis exceeds whatever osteogenesis is taking place.

In long-standing osteoporosis, calcium excretion is within normal limits. Presumably, depletion of the skeleton progresses just to the extent of stimulating osteoblastic activity, and this compensatory response prevents such discrepancy between bone formation and resorption as might lead to hypercalciuria. This also accounts for the normal index of osteoblastic activity—i.e., the serum alkaline phosphatase content is normal.

In spite of the diminution of bone mass in long-standing cases of osteoporosis, the serum protein values are generally normal.

Clinical Picture.

The onset of osteoporosis is usually slow and insidious—months, even years may pass before the condition will be noticed by the patient or by the examining physician.

Frequently osteoporosis is discovered either clinically by the physician, or by the radiologist during routine examination for some other condition. A frequent X-ray report reads: "There is present decalcification of bone which is normal for the age of the patient." Decalcification is never normal. To wait for evidence of compression fractures and obliteration of intervertebral spaces before making a diagnosis of osteoporosis is to subject the patient to unnecessary pain and invalidism from a condition for which treatment is so effective.

The early symptom is pain, which is of a dull, uncomfortable, aching type—not sharp. It may be vague and for a long time not definitely localized. Later, there will be in addition sluggishness, weakness and general tiredness. The patient will find it more comfortable to be sitting or lying down, and will avoid physical effort. There may be difficulty in gait, inability to use hands and arms freely and to carry on any form of activity. The patient also becomes moody, depressed and uninterested. Anorexia, insomnia and loss of weight are present, because of general atrophy of bone and muscle and loss of calcium. Kyphosis develops which involves the dorsal segment of the spine, but may also involve the cervical segment. Thinning of the hair, brittle nails and a thin, dry and scaly skin are also present.

X-Ray Findings.

Rarefaction of bone structure, predilection for the spine and pelvis, biconcave compressions and flattening of the lumbar region, wedging in the dorsal segment of the spine, marked thinning in the compact layer of bone with poor osseous trabeculæ—these form the usual X-ray picture.

Pathological fractures may be present, the vertebræ and the femoral neck being particularly susceptible.

Ætiological Classification.

Since osteoporosis is but a component in a wider symptom complex, it is essential to elucidate the pattern and track down the cause or causes. These may be classified as follows:

1. Atrophy of disuse (resulting from loss of the normal stress and strain on the skeleton):

(*a*) Immobilization—e.g., fractures, bone and joint tuberculosis, shoulder-hand syndrome.

(*b*) Paralysis of muscles pulling on the skeleton—e.g., poliomyelitis and paraplegia.

2. Nutritional disturbances:

(*a*) Influence of vitamins A, B, C, D.

(*b*) Lack of nitrogenous compounds: (i) decreased intake—malnutrition and anorexia nervosa; (ii) increased breakdown—diabetes mellitus and hyperthyroidism; (iii) malabsorption or deficient utilization—pancreatic and gastro-intestinal disease, sprue; (iv) excessive loss—nephrosis and burns.

3. Endocrine disturbances:

(*a*) Hypo-ovarian condition: congenital ovarian agenesis, castration, infection, functional, post-menopausal.

(*b*) Androgen deficiencies: castration, infection, senility.

(*c*) Excess cortisone-like substances in (i) prolonged stress and alarm reaction, (ii) prolonged cortisone therapy, (iii) adrenal hypercorticism (Cushing's syndrome).

4. Injury to bone tissue:

(*a*) Post-traumatic—Sudek's atrophy.

(*b*) Irradiation and ultra-sonic waves.

5. Developmental disturbance:

(*a*) Osteogenesis imperfecta.

(*b*) Congenital cranial osteoporosis.

6. In combination with other diseases:

(*a*) Paget's disease.

(*b*) Alkaptonuria.

(*c*) Systemic lupus erythematosus and macroglobulinæmia.

(*d*) Leukæmia.

7. Undetermined defects:

(*a*) Idiopathic osteoporosis.

(*b*) Acromegaly.

This is a provisional classification of disorders in which osteoporosis may occur. Two or more may coexist. For example, the patient may be an elderly woman, in whom osteoporosis becomes evident after operation as a result of immobilization, impaired appetite and metabolic response to surgery superimposed on post-menopausal changes.

Management.

The primary objects of treatment in osteoporosis are remedy of the causative factors and the restoration of healthy osteoblastic function. Management is concerned with alleviating pain, restoring bone structure and preventing deformity.

The time available for this paper does not permit me to deal exhaustively with each of the possible causes, but only briefly, as each of the approaches to management is discussed.

Atrophy of disuse occurs in severely bed-fast patients, and there appears to be no difference between the effect of immobilization and that of injury followed by immobilization. The extent of the osteoporosis is directly

proportional to the completeness of immobilization and the condition is more acute when it is due to disuse atrophy than to other conditions; therefore, electrolyte alterations do become evident and urinary calcium excretion increases, with possible ill effects on kidney function and even the formation of renal calculi. This is more likely to occur in children than in adults. Albright reports the case of an active boy, aged 14 years, who developed osteoporotic hypercalcæmia and decreased function of the kidneys after being immobilized for the treatment of a fracture of the femur resulting from a solitary cyst. A diagnosis of hyperparathyroidism was made, but could not be confirmed by exploratory operation. After free movement of the part, the serum calcium level fell to normal, and kidney function improved. As increased calcium intake and excessive ingestion of vitamin D promote intestinal absorption, it may be wise to curtail the intake of these substances in immobilized patients, allowing only enough to maintain a positive calcium balance. To counteract the ill effects of long-term immobilization, maximal mobility in bed with conscientiously applied exercises should be undertaken.

Dietary Considerations.

One of the keystones of therapy is a substantial protein diet. Any patient in a state of inanition is a candidate for osteoporosis. Protein may not be available because of (i) inadequate intake, (ii) malabsorption—chronic liver and pancreatic disease, (iii) excess loss—nephrosis and burns—or (iv) diversion to caloric requirements—diabetes, hyperthyroidism, excess corticoids (exogenous or endogenous).

A toxic goitre in an adult may produce simple osteoporosis from negative nitrogen balance or from the effect of the thyroid hormone on the kidney, causing increased secretion of phosphates and calcium and a compensatory osteoclastic activity of bone. Absence of insulin in uncontrolled diabetes causes a relative nitrogen starvation, because amino acids are diverted to glucose production from protein synthesis. Hernberg found osteoporosis to be a presenile change occurring fairly regularly in adult diabetics. Cortisone and allied substances are anti-anabolic, and also stimulate the rate of glucose formation from non-carbohydrate precursors. These hormones increase calcium loss by increased calcium excretion by the bowel. Many cases of osteoporosis have been reported to follow prolonged administration of corticoids.

The issue here is still clouded, because in many of these cases — for example, rheumatoid arthritis — the disease being treated predisposes the subject to bone disease. Also, it has been postulated recently that corticoids cause osteomalacia as well as osteoporosis.

When considering this cause of osteoporosis, I was reminded of a rather significant experience I had in Chicago in July, 1957. I had just attended the ninth International Congress of Rheumatic Diseases in Toronto, where a report had been given of 100 cases of fractures in vertebræ in rheumatoid arthritics treated with cortisone for long periods. Now I was visiting this doctor's clinic and he described, with great pride, the case of a second-hand-car salesman who had been kept at work (most lucratively) for five years by massive and increasing dosage of cortisone, until at last he was financially secure, but had had several gastric hæmorrhages and three fractured and collapsed vertebræ. He had to wear a big corset, was free to dose himself with as much cortisone as he liked—and was a candidate for a wheel-chair life any time. It struck me that this was an example *par excellence* of the American philosophy of life, directing treatment so that hypercortisonism—with osteoporosis and all the other complications—with financial security was thought preferable to conservative therapy and simpler living on reduced income. This British versus American approach is summed up in the verse from Ecclesiastes: "Better an handful with quietness, than both hands full with vexation of spirit."

Effect of Vitamins and Minerals.—Hypervitaminosis has been reported to cause osteoporosis and is reversible. Deficiency of vitamin C causes scorbutic osteoporosis, which is due to a general paucity of cement substance—the collagen fibres in the matrix are not elaborated. Moderate amounts of calcium and vitamin D are indicated, because the net mineral loss in osteoporosis may be considerable. Copper deficiency has been found to cause osteoporosis in dogs. On an ideal protein-rich diet with adequate calcium, phosphorus, vitamin and hormone intake, maximal retention will not exceed two grammes of calcium per day. Therefore, it will require at least nine years to return a normal X-ray picture.

Endocrine Disturbances.

Osteoporosis is observed in the hypopituitary state either before or after puberty. The exact role of the pituitary in the development of the osteoblast has not been determined. The administration of growth-stimulating principle leads to proliferation of osteoblasts and appearance of new bone matrix.

Sufficient cases of osteoporosis following artificial or natural menopause have been observed to suggest that ovarian function may be at fault. The classical studies of Albright and Reifenstein on "post-menopausal osteoporosis" brought about much of the present interest in osteoporosis in general, and pioneered gonadal hormones in treatment of this condition. Post-menopausal osteoporosis refers to the condition under the age of 65 years; senile osteoporosis comes after 65. This chronological differentiation is arbitrary and bears no relation to the clinical situation. Acceptance of the concept that post-menopausal and senile osteoporosis are the same condition and that hormone deficiency is the cause will contribute much to diagnosis and treatment.

"On the average, the onset of osteoporosis is about 9 years after artificial menopause" (Albright). In Anderson's series the onset is one to 17 years after the artificial menopause.

In patients aged 40 to 60 years, osteoporosis occurs almost exclusively in women, and in the older group four times as often as in men. The value of sex hormones in osteoporosis lies in their diverse effects on bone metabolism: they have a general anabolic action and stimulate the growth of all tissues including osteoid. The effect of androgen on nitrogen retention is more sustained than that of œstrogen. Both hormones decrease urinary and fæcal excretion of calcium and phosphorus in all cases of osteoporosis except the idiopathic type. This effect is greater with œstrogens than with androgens. The serum level of inorganic phosphorus in post-menopausal osteoporosis is often high, and falls during the administration of sex hormones. The alkaline phosphatase level is not influenced by gonadal hormones except during treatment of Cushing's syndrome with androgens. Œstrogens are believed to have a special stimulating effect on osteoblastic activity.

Osteoporosis, therefore, is not caused by the improper distribution of calcium or by the loss of calcium, but by an inability of the utilization of the calcium present because of insufficient matrix formation to absorb and retain the calcium from the intercellular fluid.

As the hormone deficiency continues, imbalance between bone formation and bone destruction increases, and is further aggravated by the enforced immobilization which accompanies the osteoporotic state, depriving the bone mass of restorative benefits derived from the muscular stress and strain produced by activity.

Hormone Therapy.—Hormonal therapy gives osteoporotic patients a new lease of life. The most striking effect is on pain. They become animated and eat better, but objective improvement is very slow. The osteoporosis begins to regress, but X-ray proof is not discernible for years. Hormonal therapy, however, has its hazards. The high incidence of uterine bleeding accompanying œstrogen therapy can be very distressing. Mammary and pelvic congestion often occurs. Also, there is the unanswered question of the role of œstrogens in tumour formation.

Androgens in large doses cause virilizing changes in women. (This leads to lack of cooperation.) Electrolytic imbalance can occur, with œdema. To overcome these ill effects, simultaneous administration of both hormones is often used; but it is difficult to strike the proper ratio between the two. There is a growing trend nowadays to employ the newer, less virilizing androgens, and several reports on methylandrostinediol show a satisfactory response in 80% of cases. Because osteoporosis appears to be a concomitant of advancing years, it has been advocated that all women should receive hormones prophylactically, but there do not appear to be any reported studies in the literature.

The doses are as follows: (i) for women, 1 to 5 mg. of stilbœstrol per day, with 25 mg. of testosterone three times a week by intramuscular injection, treatment to continue for periods varying from six weeks to three months; (ii) for men, 50 mg. of testosterone three times a week, with 1 ampoule of "Primordian-Depot" (65 mg. of testosterone œnanthate and 4 mg. of œstradiol valerianate) every two to three weeks. Anderson found 0·9 mg. of "Dienœstrol" per day effective, and it could even be given for long periods without causing uterine bleeding.

Strontium.—Strontium acts apparently as an additive mineralizing factor by enhancing calcium absorption and storage. How it does this is unknown. However, it is important to remember that unless there is sufficient phosphorus intake, strontium will compete with calcium and protein for the available phosphorus, since it is utilized only as the phosphate.

Shorr and Carter reported that the sum of strontium and calcium retained (with a constant phosphorus intake in post-menopausal osteoporosis) was greater than the maximum retention of calcium when it was given alone.

Fraser and co-workers described a strontium infusion test which may prove to be useful to elucidate obscure cases. A single intravenous injection of strontium is given, and concentrations in urine and serum are followed for several days. Strontium is used as a tracer to indicate calcium uptake by the bone.

Analgesic and Other Supportive Measures.—Salicylates are useful in curtailing discomfort. "Butazolidin" has been given along with sex hormones; but it is doubtful whether it adds anything, and, it can have harmful side effects. Sedatives should be used with discrimination in the geriatric patient; barbiturates often have a prolonged effect because of lessened permeability of the kidney.

It is questionable whether intraganglionic injections of alcohol and nerve section are ever warranted except as a last resort.

Control of local and radiating pain is promoted by physiotherapy and orthopædic rehabilitation, through active and passive exercises.

Suitable spinal supports should be used, but only for short intervals; they should be used for longer intervals only in the treatment of patients with pronounced deformities not corrected by other means. Massage and moderate heat help in relaxing muscle spasm. Short-wave diathermy is thought by some physicians to aggravate osteoporosis because of hyperæmia; others challenge this.

Aside from the taking of a balanced diet with supplementary food concentrates, blood transfusions are useful in raising body resistance and providing readily usable protein.

It is important to avoid sleeplessness, tension, anxiety and exhaustion and infections, since osteoporosis may be aggravated by these disturbances presumably via the stress syndrome.

Differential Diagnosis of Post-Menopausal Osteoporosis.

Before a diagnosis of post-menopausal osteoporosis can be accepted, all other conditions causing decreased density of bone must be excluded. These are most likely to be osteomalacia, myeloma, malignant metastases, hyperparathyroidism, Cushing's disease and hyperthyroidism.

Osteomalacia produces a calcium deficiency, and in the radiological picture the bone shows deficient lines of mineralization. There is a low blood calcium level with decreased calcium excretion in the urine. When hyperparathyroidism, myelomatosis or metastatic malignant disease causes a diffuse rarefaction of the skeleton, the diagnosis may be difficult.

In hyperparathyroidism and myelomatosis, the blood values may be significant—raised serum calcium, raised alkaline phosphatase and low inorganic phosphorus levels in the former, and hyperglobulinæmia in the latter. Sometimes in myelomatosis there is a raised serum calcium level, with normal alkaline phosphatase and inorganic phosphorus levels. Excessive excretion of calcium and phosphorus as shown in balance studies may be present in both myelomatosis and the early stages of post-menopausal osteoporosis.

Sternal puncture may be advisable to exclude myelomatosis, especially if the erythrocyte sedimentation rate is raised. If idiopathic steatorrhœa is suspected, fat-balance studies should be carried out.

Thus, the position may be summarized as follows: If the serum calcium, phosphorus and alkaline phosphatase levels are normal and there is evidence of bone demineralization, the likely diagnosis is osteoporosis. Whenever anæmia, a low calcium or phosphorus level, an elevated alkaline phosphatase level or an elevated serum globulin level and a negative calcium balance are present, a search for pathological conditions other than post-menopausal osteoporosis as the cause of demineralization should be made.

Cushing's syndrome is no problem except in its early stages. It has its own characteristic symptoms, signs and pathology. The osteoporosis of Cushing's syndrome is ameliorated by testosterone and œstrogens—the former to counter the anti-anabolic corticoids and the latter to restore calcium balance.

In acromegalic osteoporosis the pathogenesis is intricate, being contributed to by excessive growth hormones, secondary hypogonadism, hyperthyroidism and diabetes. Benefit is obtained by the use of gonadol hormones. In *fragilitas ossium*, the hereditary form characterized by thin skin, thin cornea, thin blue sclera, severe osteoporosis, defective tooth development and deafness, a positive calcium balance and clinical improvement can be obtained with both sex hormones.

Sometimes after a bone has been fractured a rapid loss of bone tissue may result, either at the site of fracture or distal to it. This is known as Sudeck's atrophy or post-traumatic osteoporosis. The injuries and diseases in which this condition develops are those causing spontaneous or therapeutic immobilization of an extremity. The management of these cases is by as early and as complete mobilization of the extremity as possible and physiotherapy.

Osteoporosis may be superimposed on Paget's disease, and it is particularly important in immobilization of these patients—for example, after a fracture—to give vitamin D, calcium and hormones.

Osteoporosis may also occur with systemic lupus erythematosus, and require treatment apart from the lupus.

In certain diseases characterized by extraneous cells in the marrow spaces—for example, leukæmia, multiple myeloma, macroglobulinæmia and congenital syphilis—true osteoporosis may be present. Therapy consists in dealing with these cells, and is unfortunately not very satisfactory in any of these conditions.

In some cases of unusual osteoporosis none of the foregoing causes can be traced. In men, the osteoporosis may follow a seemingly insignificant accident and be without antecedent symptoms; in women, after a normal pregnancy osteoporosis may occur. It is usually severe, with backache, compression fractures and extensive radiographic changes in the spine. Conventional therapeutic measures have proved valueless. The sole effective agent is serum albumin given intravenously. Albright and his

co-workers adduced from their metabolic studies that albumin may be a transport form of bone matrix precursor. Reifenstein has suggested the possibility of giving a course of albumin therapy at the time when a patient with severe post-menopausal osteoporosis is started on steroid medication. This deserves investigation.

Conclusion.

In conclusion, I should like to emphasize that osteoporosis is a prevalent condition that should not be overlooked. Treatment in most cases is effective and gives considerable relief to the afflicted. It should be instituted and carried out whenever osteoporosis is suspected.

A prophylactic hint is given by Edmond J. McDonnell: "Elderly ladies should avoid heavy lifting and should be squeezed gently."

Reports of Cases.

DYSTONIC REACTION TO PERPHENAZINE ("TRILAFON").

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PERPHENAZINE ("Trilafon") and prochlorperazine ("Stemetil") are becoming widely used as anti-emetic drugs in both general and obstetric practice. Perphenazine and related phenothiazine derivatives are used in psychiatric practice.

Two previous cases of dystonic reaction to perphenazine have been reported in which small doses were given for hyperemesis gravidarum.

The following case is of interest because it emphasizes the smallness of the dose which will produce the dramatic and bizarre picture in a susceptible person; because it confirms the symptom-specificity of the abnormal reaction to drugs of this type; and because, in this patient, the symptoms were reproduced after a normal interval when a further small dose of the drug was taken. It also draws attention to the diagnostic difficulty presented to the doctor unaware of a reaction which may become more prevalent as these drugs are increasingly used.

Clinical Record.

The patient, a girl, aged 20 years, had reported to her general practitioner for ante-natal care. She was two months pregnant, and had vomited throughout the second month. Perphenazine in a dosage of 4 mg. twice a day, was prescribed. She took one tablet that night, and a second the following morning. Twelve hours later the practitioner was called, and such was the degree of spasm of the patient's facial muscles that he wondered whether she had dislocated her temporo-mandibular joints. He also noted spasms of head retraction and sent her to the Queen Elizabeth Hospital, where the casualty officer found no dislocation of joints, thought her hysterical, and sent her home. The spasms continued variably throughout the night, and in the course of the next day, her doctor's partner was called and gave her some pethidine, which brought relief. He was called again in the evening, and became so concerned that he referred her to the hospital once more.

When the patient was examined on this occasion, her head would slowly turn, first to the left and then to the right, and become fixed. At other times it retracted slowly. Her eyes at intervals became fixed and staring, but did not roll up. Her speech was slurred (she complained of a "stiff tongue") and her jaws clenched from time to time as in tetanic trismus. She moved the rest of her body freely and had no tremor or other evidence of neurological disorder. She had no headache, but said that she had a feeling of tightness in the face and neck. However, as each manifestation appeared it was notable that it could be abolished by command, only to be replaced by a spasm of another group. Occasionally, she appeared oblivious to question or command, but would respond after an interval. Her symptoms were thought to be hysterical in origin.

After she had been admitted to hospital for observation, the patient's eyes closed and she was unable to open them despite strenuous efforts with her own finger and thumb. She appeared distressed and frightened at this time, and wept. She had at least one episode of head retraction and opisthotonus in the course of the night. By morning she seemed perfectly normal, and remained so during the remaining 24 hours of observation, apart from some vomiting. During this time, she said that she remembered all the events of the preceding 36 hours perfectly clearly, and that she thought she could have controlled the spasms, but did not have the desire to do so except under pressure. She had found the whole experience rather frightening.

The patient returned to the care of her doctor, who, after a few days, because of continued vomiting, suggested she should resume taking the perphenazine. Within 24 hours all the symptoms and signs already described reasserted themselves, and it became clear that they were an acute reaction to the drug.

Comment.

Chlorpromazine ("Largactil"), perphenazine ("Trilafon"), prochlorperazine ("Stemetil") and trifluoperazine ("Stelazine") are all phenothiazine derivatives, the three last mentioned containing piperazine and being closely related.

Dystonic reaction to perphenazine has been reported previously (Shanon *et alii*, 1957). Montgomery and Sutherland (1959), in Jamaica, described a reaction which followed a dose of 12 mg. of the drug, the symptoms they described bearing a striking resemblance to those noted in this case. Sandford (1959) noted two cases in Canada, and Davies (1959*a*) noted a similar reaction in a high-grade feeble-minded mental defective.

Similar reactions are reported by the manufacturers of prochlorperazine, and more recently Davies (1959*b*) reported two further identical reactions in psychiatric practice following the use of trifluoperazine ("Stelazine").

It is interesting that a similar episode should have been reported as following ingestion of chlorpromazine, particularly when the large amount of chlorpromazine which has been taken throughout the world is considered. This case was reported by Hare (1958), and the episode followed the swallowing of 600 mg. in a morning, a significant overdose.

The manufacturers of perphenazine mention muscle spasm as a possible complication of high dosage of the drug, but stress the low toxicity in recommended dosage.

Boyd (1959) reported the case of a woman aged 77 years, who swallowed 30 four-milligramme tablets of perphenazine. She remained fully conscious, but drowsy; there were no physical abnormalities at the time, and no complications ensued.

These dystonic reactions, then, appear to represent a specific idiosyncratic response to a small dose of the drug by a susceptible person. Three of the previously reported cases occurred in otherwise healthy people.

The reaction to these related drugs appears to be identical in each case, and to differ from the neurotoxic effects reported to have followed ingestion of piperazine (Combes *et alii*, 1956; Hannah, 1958).

It would be interesting to know why this reaction seems to be more common with the newer phenothiazine derivatives than with chlorpromazine, and more particularly, why the dystonia is so remarkably limited almost completely to the muscles of the cranial motor nerves, thus resembling tetanus.

The reaction, frightening to both patient and doctor, is likely to be seen more often in the future, and early recognition will comfort both.

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AN UNUSUAL CASE OF STRANGULATED ECTOPIC TESTIS.

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Embryology.

THE testis is developed on the posterior abdominal wall close to the developing kidney. By the end of the third month the testis has descended to lie retroperitoneally at the point where the inguinal canal is being formed. It remains at the abdominal end of the inguinal canal until the seventh month, when it descends through the inguinal canal to reach the scrotum by the end of the eighth month. Descent may be arrested along this path (imperfectly descended testis), or the testis may descend but occupy an abnormal position (ectopic testis). An imperfectly descended testis is commoner on the right side than on the left, and is often associated with a congenital hernia.

Clinical Record.

A male patient, aged 34 years, presented on June 3, 1958, with a painful swelling in the right inguinal region about one inch lateral to the deep inguinal ring. The swelling had been present for 24 hours, and had grown a little larger and more tender. There had been a similar episode 12 months previously, and on that occasion the swelling had been smaller and less painful and had disappeared spontaneously after one day. He had had an operation for right inguinal hernia 12 years previously. On examination of the patient, two scars were noticed in the right inguinal region: one was the usual herniorrhaphy scar, and the second was a shorter scar placed more laterally in the iliac fossa with the swelling occurring behind it. The swelling was subcutaneous, approximately of the size, shape and consistency of a testis, and tender. The right testis was absent from the scrotum, but the left testis was present. The swelling was considered to be a superficial inguinal ectopic testis with torsion, and operation was performed the same day.

At operation, a strangulated testis was found in the subcutaneous tissues, accompanied by a small peritoneal sac. The sac and the greatly attenuated spermatic cord pierced the external oblique aponeurosis through a fibrous-edged opening approximately 0·5 cm. in diameter, and were fairly firmly adherent to the edges of this opening. It was at this point that strangulation had occurred, and when the aponeurosis on either side of the sac and cord had been incised, the testis soon assumed a healthy pink colour. The sac and cord similarly pierced the internal oblique and transversus abdominis muscles, and were found to be issuing from a greatly enlarged deep inguinal ring which appeared to have been rent in a lateral direction, so that it was two to three times the normal size. The sac being empty, it and the cord were ligated together and, with the testis, were excised. The deep inguinal ring was obliterated by oversewing, and the muscles and aponeurosis were repaired.

The pathologist's report on the testis was as follows: "The specimen is a testis showing marked degenerative changes in the tubules. Marked vascular congestion and interstitial hæmorrhage are present. There is no evidence of malignancy."

Subsequently, contact was made with the surgeon who had performed the earlier operation, and he stated that, in repairing the indirect hernia, he had invaginated the sac into the abdomen, brought it out through the abdominal wall in the iliac fossa and stitched it to the external oblique aponeurosis (hence the second skin incision). The testis was not found during the operation.

Discussion.

The method quoted of dealing with the sac in an indirect inguinal hernia was originated by Kocher (1911), who named it the transposition-invagination method, and strongly advocated it for uncomplicated inguinal hernia.

In the case discussed it seems likely that the testis was intraabdominal at the time of the first operation, and, either at operation or in the immediate post-operative period, herniated through the abdominal muscles along the path provided by the displaced hernial sac. That this event coincided with, or immediately followed, the hernia operation is suggested by (i) the small size and rigid edges of the aperture in the external oblique aponeurosis and (ii) the degree of adhesion of the sac and cord to this aperture. The large rent in the transversalis fascia suggests that, in the performance of the Kocher manœuvre, damage may be caused to the fascial borders of the deep inguinal ring, thus creating a potential weak spot through which an acquired indirect inguinal hernia can later force a path. This possibility of damage to the deep inguinal ring has been recognized by W. Heneage Ogilvie and Rodney Maingot (1937).

It is interesting to speculate on why the testis should have remained unnoticed in such a superficial position for 12 years, and why, in fact, strangulation did eventually occur. The patient is a moderately obese young man, and no doubt a generous layer of subcutaneous fat acted both as mask and as protection for the testis. He could not recall any trauma which might have precipitated the strangulation. Perhaps the cord was "nipped" by the external oblique aponeurosis during strong abdominal muscular contraction, and the resultant swelling of the cord within the unyielding fibrous aperture in the aponeurosis was sufficient to cause increasing restriction of circulation in the testicular vessels (in the manner of the too-tight plaster cast on the broken limb). Finally, it is now correct to label this testis "ectopic", although it was an "imperfectly descended" testis before herniating.

Summary.

A case is recorded in which an intraabdominal testis herniated through the abdominal wall and became strangulated after a Kocher's repair of an indirect inguinal hernia.

The possibility of damage to the deep inguinal ring by Kocher's transposition-invagination manœuvre is pointed out.

Acknowledgements.

I am indebted to Mr. J. C. Bell Allen for producing from his records of 12 years ago the details of the hernia operation; also to the Microbiological Laboratory of the New South Wales Department of Public Health for examining and reporting on the specimen; and to Miss M. Rolleston of the British Medical Association Library for finding and making available to me Kocher's "Textbook of Operative Surgery".

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NEPHROTIC SYNDROME DEVELOPING AFTER SNAKE-BITE.

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RENAL DAMAGE occurs in many fatal cases of snake-venom poisoning, tubular necrosis being the best-known lesion, although death may be due to other factors (Efrati and Reif, 1953; Jutzy *et alii*, 1953; Amorim and Mello, 1954; Knyvett and Molphy, 1959). Certain substances capable of causing renal tubular damage may also induce the nephrotic syndrome, as inorganic mercurials (Wilson, Thomson and Holzel, 1952), and possibly poison oak (Rytand, 1948) and gold (Vallery-Radot *et alii*, 1942). In recent reviews of the nephrotic syndrome (Barnett and Eder, 1957; Kark *et alii*, 1958), snake-venom poisoning is not listed as one of its many accepted causes. The following case report is presented as it appears to indicate such a causal association; but, although the case history is presented systematically, some of the early details were obtained only in retrospect.

Clinical Record.

A single woman, aged 23 years, was admitted to hospital in March, 1957, complaining of generalized swelling of the body and lower abdominal pains of four days' duration. This œdema had not been preceded by a sore throat or comparable condition. Previously she had been perfectly well. In 1955 she suffered an œdematous ear and eyelids from the bite of an unidentified insect; an insurance examination in that year did not reveal physical illness or proteinuria. Five days before her admission to hospital a "brown-coloured" snake, some few feet in length, had slithered onto her feet while she was bush-walking. Her feet were bare, except for scuffs, and the snake was clearly seen by others; as it touched her the patient became "petrified with fear". When more than two puncture marks were found on the dorsum of her right foot, it was asserted by a companion that the snake was non-venomous and, therefore, first-aid measures were unnecessary. On returning to a house, she had to rest because of weakness in her limbs and sleepiness, which she interpreted as "a nervous reaction". The bite became painful, swollen and "bruised", and the "bruise" spread. Next day, only two puncture marks could be clearly seen. Within 24 to 36 hours of the bite she became pale and experienced sharp, lower abdominal and back pains, and felt "nervy and shivery"; but there was no diarrhœa, although the fæces were "dark". During the second day, swelling started in the feet, legs and abdomen and about the eyes. On the third day, there was thirst, with increased drinking, and the urine output was moderately reduced, the urine appearing somewhat "smokey", but not red. Over the fourth day, swelling was acute and sufficient to burst the seams of a frock; nevertheless, she did not feel severely ill, only very "frightened", and there was no lassitude, headache, blurring of vision, nausea or vomiting.

On examination of the patient, she was not feverish, and her face was pale and swollen; there was marked œdema of both lower limbs, moderate œdema of the abdominal wall and lumbo-sacral area and minor œdema elsewhere; the abdomen was distended with ascites. The dorsum of her right foot was desquamating, and apparently bruised about a scab. The jugular venous pressure was not raised, the pulse rate was 84 per minute and regular, the arterial blood pressure was 140/100 mm. of mercury, but the heart sounds were not over-active. There were no tonsils, and the fauces were not inflamed or injected; the breath sounds were normal. The renal areas did not seem tender. The urine, of specific gravity 1·040 boiled solid with protein as it had done, when examined elsewhere, on the previous day; microscopic examination of the centrifuged deposit revealed 10 to 12 leucocytes, up to 20 erythrocytes and some 20 "epithelial" cells per high-power field, and numerous coarsely and finely granular casts, with occasional hyaline casts but no red cell forms, per low-power field. Initial therapy was conservative.

On the day after her admission to hospital, œdema was more evenly distributed and marked; intense facial and palpebral œdema closed both eyes, and the conjunctivæ were also œdematous. The abdomen was more distended, and tender to palpation; also, abdominal pains had returned. Both eyelids were bruised, from the patient's repeated attempts to open them, and there was also bruising elsewhere; this bruising tendency had followed the snake-bite. The arterial blood pressure was 130/90 mm. of mercury. The hæmoglobin concentration was 14·7 grammes per 100 ml. of blood; the total leucocyte count was 12,000 per cubic millimetre, with a normal distribution, and the erythrocyte sedimentation rate (Cutler) was 23 mm. in one hour; the blood urea content was 33 mg. per 100 ml. On the fourth day after her admission to hospital an electrophoretic pattern of serum proteins (see Table II) showed low concentrations of albumin and gamma globulin. The centrifuged urinary deposit then contained up to five erythrocytes, up to ten leucocytes, and one or two renal cells per high-power field, and many finely granular casts, with smaller numbers of coarsely granular casts, per low-power field.

Subsequently, the specific gravity of the urine remained high—1·038 to 1·042—and the urine continued to boil solid with protein, which scarcely settled on standing. The low urine volumes of the first three weeks are listed in Table I; but it was not until the third week, when proteinuria was decreasing according to qualitative tests, that an estimate was made of the protein loss (see Table I). The œdema was variable in distribution, and bilateral

TABLE II.

Serum Protein Levels, in Grammes per 100 Millilitres, in the First Fifteen Weeks after Admission to Hospital.

Interval.	Total Protein.	Albumin.	Globulins.			
			Alpha-1.	Alpha-2.	Beta.	Gamma.
Day 4	3·6	1·5	0·35	0·94	0·70	0·3
Week 4	3·9	<1·0	—	—	—	<0·1[1]
Week 6	4·2	1·5	—	—	—	0·1[1]
Week 10	5·8	2·9	0·36	0·96	0·90	0·2
Week 12	6·3	3·9	0·35	0·86	0·98	0·7
Week 15	6·7	3·9	0·32	0·74	0·82	0·8

[1] Inadequate separation of globulins in the electrophoretogram with dense staining of the alpha-2 globulin region.

pleural effusions developed, in addition to ascites. The blood urea content was 100 to 105 mg. per 100 ml. at the end of the second week, and 50 mg. at the end of the third week, the serum electrolyte concentrations being essentially normal (sodium, 137 to 142, potassium, 4·8 to 5·3, chloride, 96 to 103, bicarbonate, 28 to 29, mEq/l.). The appearances of the centrifuged urinary deposit altered little after the fourth day, except that the renal cells showed fatty degeneration, and small numbers of fatty casts and bodies appeared; but red cell casts were not seen at any time. The erythrocyte sedimentation rate remained elevated, 20 to 25 mm. in one hour; the blood hæmoglobin level varied from 13·5 to 15·5 grammes per 100 ml., and serial estimations did not suggest an initial hæmodilution from an increased plasma volume, as might occur in acute glomerulonephritis; the erythrocytes, leucocytes and platelets were normal in numbers and appearance in stained blood smears. Serum protein concentrations were 3·6 to 3·9 grammes per 100 ml., and the albumin and gamma globulin levels were decreased and the alpha-2

globulin content correspondingly increased; the serum cholesterol content was 415 mg. per 100 ml. in the third week. Cultures of the initial throat swabbings did not grow *Streptococcus hæmolyticus*, and a later antistreptolysin titre did not suggest a recent streptococcal infection. Also, beyond acne vulgaris, there were no skin rashes or subsequent desquamation. The Eagle-Wassermann, Kahn standard and Kline diagnostic tests all produced negative results, and L.E. cells were not found when sought on a number of occasions.

Because of continuing œdema and discomfort from it, the oral administration of 400 mg. of cortisone per day, in divided doses, was started during the fourth week; the blood urea level was then 33 to 38 mg. per 100 ml., and the serum electrolyte concentrations were normal. In addition, 45 grammes of "Katonium" resin were given on each of five successive days in each seven. Cortisone administration was stopped after nine days because of severe epigastric pain, increasing œdema and the development of a large abscess in the right thigh, at the site of an injection; but resin therapy was continued. In the fifth week an intravenous injection of 50 grammes of salt-poor human serum albumin induced diuresis, 2150 ml. of urine being passed in the corresponding 24 hours, and most within eight hours of the injection, whereas the previous daily urine volumes were 450 to 600 ml.; subsequently the urine output decreased. In the sixth week the abscess in the thigh was still causing fever and much discomfort, and œdema had increased. The daily urine volumes were then 185 to 400 ml.; the hæmoglobin value was 10 to 11 grammes per 100 ml. of blood. A further injection of 50 grammes of albumin led to diuresis with the passage of 1060 ml.; thereafter the daily urine volumes varied from 650 to 400 ml. During the seventh week the urine output started to increase progressively, and rose from 400 to 1070 ml. over two days, and to 1745 ml. over seven days; the blood urea level fell to 17 mg. per 100 ml. During the eighth week the daily urine output averaged 2730 ml., with a maximum of 3820 ml., and the protein loss was 2·5 to 3·0 grammes. This diuretic phase led to a remission of œdema; it started some three weeks after withdrawal of cortisone and a febrile reaction to an abscess, and was completed during the ninth week. The body weight fell from 150 to 112 lb. Subsequently, there was no clinically detectable œdema or ascites, no pleural fluid was seen on radiographic examination of the chest, and the daily urine volumes were 1000 to 1200 ml., containing less than one gramme of protein.

The serum protein concentrations became normal in the twelfth week, several serial values being shown in Table II. The increase in the serum albumin levels appeared to follow the decrease in proteinuria, and there was a later rise in the levels of gamma globulin and a fall in those of alpha-2 globulin. By the fifteenth week the urine was consistently free from protein, the centrifuged deposit containing an occasional leucocyte and numerous hyaline casts, but only occasionally coarsely granular casts in low-power microscopic fields. The body weight had increased to 128 lb. without œdema, and the patient felt well. Also, the electrocardiogram, which had been of low voltage with "flat" *T* waves during the œdematous phase of the illness, was now normal in appearance. Resin therapy was stopped and dietary sodium intake increased, without the reappearance of œdema.

The urine remained free from protein in the sixteenth week; its centrifuged deposit was normal on microscopic examination, and the specific gravity varied normally. The arterial blood pressure was 125/85 mm. of mercury, the hæmoglobin value was 12 grammes per 100 ml. of blood, and the erythrocyte sedimentation rate had become normal; the blood urea and serum electrolyte and cholesterol concentrations were all within normal limits. As remission, or recovery, seemed established, the patient was discharged from hospital.

She was examined one, three, six and 25 months after her discharge, and on none of these occasions was any evidence of persisting renal disease found. In addition, protein has not been detected in the urine, both on occasions of respiratory tract infections and otherwise, when tested for elsewhere.

TABLE I.

Daily Urine Output for the First Three Weeks after Admission to Hospital, Estimated Proteinuria (Esbach's Procedure) During the Third Week

Day.	Urine Volume. (Millilitres.)	Protein in Urine. (Grammes per Litre.)
1	—	—
2	400	—
3	60	—
4	260	—
5	65	—
6	135	—
7	245	—
8	295	—
9	130	—
10	180	—
11	420	—
12	285	—
13	310	—
14	370	17·6
15	310	12·8
16	270	17·1
17	280	17·2
18	300	16·0
19	375	13·2
20	265	—
21	420	12·8

Discussion.

This case history is one of some interest, but, unfortunately, the early history was not given fully for some time by the patient; she seemed troubled by the implications of snake-bite, slighting its significance, although emphasizing her intense fear ("petrified with fear") at encountering a bush snake.

Clinically, the "nephritis" seemed an unusual acute type. Hypoproteinæmia and hypoalbuminæmia, hypercholesterolæmia, intense proteinuria and œdema indicated a nephrotic syndrome; but the associated features did not suggest the usual acute glomerulonephritis with nephrotic features, or any of the commoner nephrotic processes. The possibility that a snake-bite occurred in a subject who already had a nephrotic process has to be considered. However, in review, the clinical history is that of a well woman, actively and strenuously enjoying a vacation until a snake-bite, within three days of which she became acutely ill.

In a good light the snake was clearly seen by companions and stated to be some few feet in length, "brown-coloured" and without a broad body. Identification is not possible without the specimen; the common brown snake (*Demansia textilis*) occurs in the area, the taipan (*Oxyuranus scutellatus*) does not; but other venomous snakes in the area might also be described, grossly, as "brown-coloured". The possibility of envenomation was not considered at the time, as there were more than two "bite marks"; but the later appearances suggested a failure to differentiate between teeth and fang marks, and walking after the bite would aid venom absorption. After the bite, the difficulty in walking, with staggering, the evident weakness of limbs, the feeling of coldness and the subsequent drowsiness, would suggest envenomation; the patient accepted these features as the result of her emotional distress. She did not closely examine her fæces or urine in the first three days; but abdominal pains were present within 24 to 36 hours of the bite, and severe. Additionally, a bruising disorder developed, with spontaneous and easy bruising and increased vascular fragility; in the early examinations quite large purpuric spots appeared beyond the sphygmomanometer cuff, and subsequently they were smaller. This increased vascular fragility recovered over some weeks, without subsequent evidence of a defect. Thus, there were sufficient features to suggest envenomation—the appearance of the bite with

the local extravasation of blood, the initial nervous symptoms, the abdominal and back pains, and the bruising disorder. The reaction may be regarded as unlikely by some, because it is unusual; but for any species of snake the clinical features of venom poisoning vary because of differences in individual venoms, and variable host reactions to the venom (Jutzy *et alii*, 1953).

The nephrotic syndrome following the snake-bite developed more acutely and intensely than is usual for the commoner forms of the nephrotic process, or recrudescences of a polycyclic syndrome, in which œdema may reappear quite acutely. Venom poisoning can lead to swelling about the bite and of the subject (Jutzy *et alii*, 1958); but the serum protein levels fell rapidly, which would suggest, at least, massive proteinuria (Barnett and Eder, 1957; Kark, 1959), as this was still considerable during the third week and clinical improvement appeared to be associated with its decrease. Enteric losses of protein were not considered or estimated at any time. If a causal association with snake-bite is accepted, the possible coagulant action of the venom might suggest that the renal lesion was bilateral venous thrombosis. However, a nephrotic syndrome following this lesion has seemed to be slower in developing and a raised blood urea level to persist longer if the thrombosis is extensive, and either less marked or longer continued if the thrombosis is reversible, than was the case in this patient (Harrison, Milne and Steiner, 1958; Milne, 1958). In fatal venom poisoning, particularly with hæmolysis, acute tubular necrosis is the best-known renal lesion, but there are also glomerular changes (Efrati and Reif, 1953). In this instance, it seems likely that a substance in the venom of the unidentified snake produced glomerular damage, which is the basic lesion of the nephrotic syndrome (Folli *et alii*, 1957, 1958; Kark, 1959). In view of the elevated blood urea levels, glomerular changes may be considered greater than a simple increase in permeability; but this is not necessarily so (Folli *et alii*, 1958), although their nature remains speculative, as renal biopsy was not undertaken. The relationship between the substance damaging the endothelium and that affecting the glomerulus, if any, is unknown. There was nothing to suggest that the process was a hypersensitive or allergic one, nor was there previous envenomation (Parrish, 1957), as has been described with bee-stings (Barnett and Eder, 1957; Rytand, 1955) and pollens (Squire, quoted by Kark *et alii*, 1958) respectively. In retrospect, it is unfortunate that an enteric loss of protein was not thought possible and investigated (Gordon, 1959), in view of the abdominal pains and venom action, but the rapid fall in the serum protein levels indicates a basic nephrotic process.

On the evidence of this case history, snake-venom poisoning would seem another causal association with the nephrotic syndrome, venom containing a potentially noxious stimulus for the glomerulus and tubules (Folli *et alii*, 1958). On this occasion the process appeared self-limited.

Summary.

A history is presented of a case of nephrotic syndrome developing acutely after a snake-bite, in which there was convincing evidence of envenomation. The snake was not identified.

The evidence suggests a causal relationship between envenomation and the nephrotic process, so that snake-venom would seem an additional possible cause of the nephrotic syndrome.

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Reviews.

An Introduction to Medical Genetics. By J. A. Fraser Roberts, M.A., M.D., D.Sc., F.R.C.P.; Second Edition; 1959. London: New York, Toronto and Melbourne: Oxford University Press. 9½" × 6½", pp. 273, with 107 illustrations. Price: 59s. 3d.

UP till quite recently the general public took little interest in the genetical conditions which determine the physique and health of children. They had heard some gossip about "bleeders", and they had an exaggerated fear of the results of cousin marriage. More than one factor has swung public opinion round to a realization of the importance of the study of heredity; but without doubt the most important has been the dramatic success of medical intervention in Rh erythroblastosis. To have the welcome baby snatched from the very articulation of death by a skilled transfusion makes a deep and lasting impression on parents and their friends and neighbours. Young couples contemplating marriage or parenthood are now genetically conscious, and the great point to remember is that they will go to the family doctor for advice and not to the scientific geneticist; nor will they be content with the counsel given by "Aunt Charlotte" in a newspaper, who is so often a crudely masculine journalist. Hence the necessity for the family doctor to be in a position to advise wisely, and hence the necessity for a book like this, which gives the important or at any rate the useful principles of hereditary transmission, even though such knowledge adds to the Atlantean burden carried by the general practitioner and medical student. A second edition of J. A. Fraser Roberts "An Introduction to Medical Genetics" now appears after an interval of 19 years. The book may be said to be rewritten, for progress in this branch of science moves quickly, necessitating revision of publications from time to time. The author captures the interest of the medical reader at once by choosing illustrative matter drawn from human case histories; there is no reference to fruit fly, bread mould or maize cob—not that these have failed to make outstanding contributions to the science, but the medical pupil cannot avoid being impressed by the eminently practical nature of the purely human occurrences cited.

The appropriate laws of heredity are given clearly and convincingly; the conventional method of presenting pedigrees is followed, but the underlying transmission of genes is made exceedingly clear by "chromosome diagrams" which we believe to be original, and if this is the case, they bring credit on the author. The recently advocated custom of giving perplexed inquirers a numerical estimate of the probability, or what may be termed the odds, instead

of a rigid prediction of danger or safety, is commended. One of the happiest tasks of the family doctor is to allay suspicions and self-accusations when an abnormal child is born.

> One explains how we all carry hidden, harmful, hereditary factors, but that most of us have the luck to marry someone who carries not our own particular brand but some other kind instead. Every now and then, however, just by sheer bad luck two people happen to marry who carry the very same harmful hereditary factor; then there is one chance in four that the factors will come together and the child suffers from the disease.

Marriage of first cousins, it is pointed out, is a smaller risk than the marriage of a Rhesus positive man to a Rhesus-negative woman. Stress is laid on the variability of expression which is a feature of dominant genes. An illustrative example is that of a woman whose sole abnormality was a cleft left hand with a missing middle finger and a flexed ring finger; two of her children had leg deformities so gross that amputation was necessary. A timely warning is given that it is only in rare conditions such as blood grouping that hereditary transmission is unaffected by environmental happenings.

This book is, as the author insists on stating, an introduction merely—that is, it is an elementary exposition, but still giving the medical practitioner the essentials. It is just possible that as research remains active and complexities are multiplied, the day will come when medical genetics will be a branch of specialization within the medical profession demanding almost exclusive concentration of study.

The School Health Service. By S. Leff, M.D., D.P.H., and Vera Leff; 1959. London: H. K. Lewis & Company, Limited. 8½" × 5½", pp. 324, with 2 illustrations. Price: 30s. (English).

This, the latest addition to the authors' works on various aspects of social medicine, will fall gratefully into the hands of many health department doctors and nurses in Australia. It is, in effect, a *Festschrift*, marking the fiftieth anniversary of the creation of a nation-wide school medical service in Britain. There was a surprisingly short interval between this event and similar ones in Australia; for instance, Victoria celebrated hers only two years later.

Apart from this, the book is of topical interest because of the criticisms currently aimed at school medical services. These are based either on the proposition that everyone can now afford medical care, or that the correlating of the results of school medical examinations with those for entry into national military service has shown a 50% diagnostic failure in the former. The book provides little verifiable material upon which arguments for or against the continuance of school medical services could be elaborated. It is, however, wholeheartedly in favour of these services.

A readable but sombre description of social and economic conditions as they affected children of school age during the nineteenth century is followed by chapters upon special problems and the services they have evoked. School dental services, the identification and management of the maladjusted child, the detection of visual and other handicaps and health education all receive some attention. The section on handicapped children is especially good.

As a cursory description of 50 years of social change, reflected in the schools, the work has considerable value. For those engaged in school medical work in Australia it has its consolations. As a book for one's private shelf, it has good but only limited appeal.

The Molecular Basis of Evolution. By Christian B. Anfinsen; 1959. New York: John Wiley & Sons, Limited. London: Chapman & Hall, Limited. 9" × 5½", pp. 244, with 99 illustrations. Price not stated.

One of the exciting developments in biological research over the past decade has been the development of the concept that genetic phenomena and protein synthesis are closely tied up together. A biochemist, if he is to understand fully the field of protein formation, must concern himself with the literature of a whole range of sciences which previously were virtually independent of one another. The studies on pure genetics, cell cytology, bacteriophage and virus action, nucleic acid structure, protein structure and intermediary metabolism all converge on the central theme of the biological formation and function of specific proteins.

In this book the author has, for the first time in a volume of this kind, attempted to look at the field as a whole and select the most fundamental information from all these different approaches. The result is an extremely useful and fascinating account of this most important field. The book opens with a brief discussion of evolution and genetic principles, and moves on to the concept of the gene controlling the synthesis of a specific enzyme. The structure of DNA and the action of bacteriophage are dealt with in a very clear fashion, and the remainder of the book deals with many aspects of protein structure, function and synthesis. A final chapter deals in a speculative fashion with the possible relationship of all this to evolution.

In spite of the wide coverage the author is seldom superficial, and many elegant practical techniques are described. However, in order to present this range of material within a limited space, the author has assumed a fairly advanced knowledge of general biochemistry. For this reason the book will probably appeal mainly to the biochemical research worker or advanced student.

The book is commendably up to date, some references being to 1959, and in spite of dealing with a rapidly advancing field of research, will probably serve as a valuable account of the fundamentals for a number of years to come.

Basic Bacteriology: Its Biological and Chemical Background. By Carl Lamanna, Ph.D., and M. Frank Mallette, Ph.D.; second edition; 1959. Baltimore: The Williams and Wilkins Company. 9" × 6", pp. 868, with many illustrations and tables. Price: £7 8s. 6d.

Students who already know the first edition (1953) of this excellent text will welcome the second. This edition has increased from 677 to 853 pages and all chapters have been expanded, but particularly those dealing with genetics and metabolism. The major divisions of subject matter are retained. The book first considers the physical structure of cells, how this is demonstrated and the theory behind staining and indicator dyes. It also discusses the effect of physical factors and chemical disinfection on cells. The remainder of the book is devoted to nutrient requirements and the passage of nutrients into the cell, and to a very full discussion of intermediary metabolism and of the genetic apparatus of bacteria.

Throughout the book the properties and capabilities of bacteria are set out to provide a basis for explaining or predicting the behaviour of a particular organism when exposed to some physical condition or particular substrate or chemical compound. Those interested in methods for the control of bacterial growth, disinfection, the effect of antibiotics and the emergence of drug-resistant mutants would find this book a reliable source of basic information. From this knowledge, a more rational planning of experiments and clinical trials could be made.

For both the research and applied bacteriologist, each chapter is a valuable review, with a bibliography to original papers up to 1958 accompanying each chapter; for example, the chapter on bacterial metabolism has about 220 references.

Readers wanting details of the isolation, identification, classification, epidemiology, etc., of particular pathogenic organisms will not find them here, nor is there any discussion of their antigenic properties.

The writing is particularly clear, and the authors take care to define their technical terms concisely; but readers may be puzzled by words like "stabile" and "happenstance" which are dotted through the text. This, however, is a mere quibble, and the book is highly recommended to all who are seriously interested in bacteria as living cells.

Books Received.

[The mention of a book in this column does not imply that no review will appear in a subsequent issue.]

"Eritroenzimopatie ed anemie emolitiche", by U. Carcassi; 1959. Pisa: Edizioni Omnia Medica. 9¾" × 6¾", pp. 376, with illustrations. Price not stated.

"Xylocaine: The Pharmacological Basis of its Clinical Use", by Sten Wiedling; 1959. Stockholm: Almqvist Wiksell. 8" × 5", pp. 146, with 24 figures and many tables. Price: Sw. kr. 20.

The Medical Journal of Australia

SATURDAY, APRIL 2, 1960.

WORLD HEALTH DAY.

THE constitution of the World Health Organization came into force in 1948 on April 7, and that day is observed each year as World Health Day. For 1960 the theme chosen for the day is "Malaria Eradication—A World Challenge", a theme which has been prominent in WHO thinking and activity for some time. The policy of eradication of malaria throughout the world was adopted by WHO in 1955, and the considerable progress that has been made since then was summarized in these columns recently.[1] It appears that eleven countries previously affected have achieved eradication of the disease; others are on the way. Nevertheless, there is a long way to go yet, and a vigorous and widespread effort will be necessary if the object is to be attained in a reasonable time. The matter is undeniably urgent. As the Director-General of WHO, Dr. M. G. Candau, has said, the campaign, especially against the mosquito, must be carried through while the weapons are still effective. Malaria remains a constant threat to more than one thousand million human beings, people who for the most part already have more than their share of sickness and poverty, and can least afford to be further weakened in their struggle against misfortune. In many cases the challenge is more to the governments of their own countries than to the rest of the world, for despite the tremendous efforts in many places, a beginning has not yet been made in 56 countries and territories with two hundred million inhabitants.

Professor G. Macdonald, Director of the Ross Institute of Tropical Hygiene in London, and chairman of the last WHO Expert Committee on Malaria, has expressed the view that the world cannot claim to be finally rid of malaria until the very last case has been detected and treated, and the infection has completely disappeared. This is a logical view, but it sets a stiff task. Its accomplishment demands knowledge of how to do it, the means to do it with and the will to carry it through. We have the knowledge. The means depend primarily on money, which must come partly from the governments of the countries concerned, partly from the world's resources, for it is everyone's responsibility. It will need a great deal of money, millions of pounds; but the cost is small in terms of human life and welfare, as it is estimated at less than one dollar for each human being freed from the menace of malaria. The will to carry it through obviously needs to be stimulated in all countries, whether malarious or not, and that is the object of this year's World Health Day.

[1] MED. J. AUST., 1960, 1: 96 (January 16).

A CONVENTION FOR GENERAL PRACTITIONERS.

THE Australian College of General Practitioners is, as we have said on a former occasion,[1] an academic body, composed of and conducted by active general practitioners or former general practitioners. Its primary concern is to ensure that the medical care brought to the public by the group in the profession which it represents is as good as it can be. This may be seen from the following stated objectives and purposes of the College: (i) To promote and maintain high standards of the general practice of medicine and surgery; (ii) to encourage and assist young men and women in preparing, qualifying and establishing themselves in general practice; (iii) to preserve the right of the general practitioner to engage in medical and surgical procedures for which he is qualified by training and experience; (iv) to assist in providing post-graduate study courses for the general practitioner; (v) to advance medical science and private and public health; (vi) to contribute to research and preventive medicine. This constructive charter follows closely on the lines of activity of the parent College in the United Kingdom, of which the *British Medical Journal*[2] wrote recently: "The rapid growth of the College in the first six years of its existence has reflected a real renascence in general practice, and is a monument too to the wisdom and enthusiasm of those who have principally guided its destinies." There seems every reason to believe that like satisfaction will be able to be expressed with the young Australian College as it gets into its stride.

Not the least important part of the College's programme is the active encouragement it gives to post-graduate study. Indeed, it is required of a member of the College, if he is to retain his membership, that he must spend an adequate and acceptable period each year in post-graduate training. To this end the College makes it its business to provide courses and other opportunities for study which are specifically tailored to general practice and its needs, and are in addition to facilities provided by the various post-graduate committees, the British Medical Association, the teaching hospitals, other Colleges, and so on. Thus the general practitioner cannot plead lack of facilities as an excuse for not abiding by Osler's dictum that medicine is a life-long study. Two excuses, however, that he may well plead are lack of time and difficulty in getting away from his practice, and it is obvious that the College had these problems in mind when it planned the General Practitioners' Convention to be held in Melbourne from October 10 to 15, 1960. If lack of time is the issue, a pleasant and comfortable meeting place, an attractive social programme and a stimulating scientific programme unite to take the sting out of having to combine study with a holiday. A special committee to help supply a

[1] MED. J. AUST., 1959, 1: 843 (June 20).
[2] *Brit. med. J.*, 1960, 1: 716 (March 5).

locum tenens where one is needed eases the difficulty of getting away from a busy practice. Details of the Convention have, we understand, been sent to doctors throughout Australia, so there is no need to repeat them here, but we must congratulate the College on the imagination it has shown in its planning and hope that the Convention will be well attended and successful in every way.

One comment, which will be obvious to most people, should nevertheless be made. It is simply that conventions such as this, admirable and commendable as they are, are no substitute for the triennial Australasian Medical Congresses of the British Medical Association; nor, we are sure, are they meant to be. The next Congress is to be held in Adelaide in 1962—a year after its scheduled time because of the meeting of the B.M.A. in New Zealand in 1961. It is reasonable to expect that it will be the first Congress of the Australian Medical Association, and we may confidently hope that all Colleges and other medical bodies in Australia will so arrange their programmes during the year of this and subsequent Congresses that these gatherings will increasingly fulfil their most important function, that of bringing the whole medical profession together. Meetings of the Colleges and other bodies are valuable and necessary, catering as they do for the special needs of the various sections of the profession. The triennial meetings of the Australasian Medical Congress, however, are vital to our healthy existence as a profession, since they provide the one opportunity for all sections not only to receive but to give in the common promotion of good medicine.

Current Comment.

SONNE DYSENTERY.

PROBABLY few realize that *Shigella sonnei* is a relative newcomer on the epidemiological stage. This bacillus was first described in Denmark in 1915, but was not recognized in Britain till about 1924. In 1924 and 1925 only 300 to 400 cases of bacillary dysentery were notified in England and Wales, but since then the incidence of the disease has steadily increased. In 1944-1945 the first big epidemic wave occurred, with the notification of over 16,000 cases in the second of these years; in 1950-1951 a still larger epidemic occurred, and a third wave reached a peak of 49,000 notifications in 1956. As Sonne dysentery is often a mild complaint, it may be assumed that notifications are very incomplete, but there seems to be no doubt that these figures represent a very marked increase in the prevalence of the disease. This rising tide of dysentery has apparently been largely if not entirely due to the increase in the number of Sonne infections, and has been accompanied by changes in the epidemiological pattern of bacillary dysentery. In 1949, an inter-epidemic year, there were 4500 cases of bacillary dysentery notified, and *Sh. sonnei* already accounted for 88% of the cases in which pathogens were isolated.[1] Since then *Sh. sonnei* has made up 96% to 97% of all isolations of dysentery bacilli. The emergence of *Sh. sonnei* as the predominant pathogen involved is no doubt the explanation of other changes in the epidemiology of the disease. Bacillary dysentery was formerly mainly a disease of rural areas, associated with inefficient methods of excreta disposal, but in Britain it has now become predominantly a disease of the great cities. In recent epidemics, though other intestinal diseases such as *Salmonella* infections occur mainly in the summer, the peak incidence of bacillary dysentery is now in the second half of the winter. It is predominantly a disease of young children, and spreads easily in nurseries and primary schools. In a paper read before the Royal Society of Medicine three years ago, Ian Taylor[2] remarked that "at a time when the intestinal infections as a group have come nicely under control, Sonne dysentery has entered a phase of wild and quite uncontrolled epidemicity", and nothing has happened since then to cause one to modify this statement. These facts are taken to indicate that in Britain the disease is now spread almost entirely by direct or indirect personal contact and that food contamination is no longer an important factor; lavatory fittings have replaced the kitchen as the focus of attention in efforts to combat the disease. Substantially the same views have been expressed by G. N. Cooper in Australia.[3]

It is plain that control of the disease presents a serious problem which has so far defied solution. According to an article in the "Current Medical Research" section of the Medical Research Council's latest annual report,[4] one factor which has hampered study of the mode of spread of Sonne dysentery has been the lack of a suitable method of typing the organism. Serological typing was found to be impossible because of the lack of antigenic differences between strains. Other methods of typing such as phage typing and determination of the sensitivity to different sulphonamides have been tried, with limited success, but little progress was possible till the development of a new method of typing was worked out by J. D. Abbott and R. Shannon.[5] This method depends on identifying the strains by the colicines which they produce. ("Colicine" is a term originally coined to denote the antibacterial substances elaborated by many strains of *Escherichia coli*, but now extended to include similar substances produced by other intestinal bacteria.) Abbott and Shannon first tested their strains of *Sh. sonnei* for their sensitivity to colicines produced by strains of *E. coli*, but this was found to be inconsistent. They then developed a technique by which strains to be investigated were tested for their production of colicines active against other strains of *Sh. sonnei* of known susceptibility. These colicines are evidently highly specific substances, most sensitive strains being sensitive to some but not to others. In their later work Abbott and Shannon used 14 different sensitive strains of *Sh. sonnei* and *Sh. schmitzi* which permitted the identification of a great variety of patterns of colicine production. Furthermore, these patterns of colicine production were found to be remarkably constant for individual strains. The main weakness of colicine typing lies in the fact that about one-third of all cultures examined produced no colicines and therefore could not be typed by this method. However, there is no doubt that colicine typing represents a great advance in the study of the Sonne bacillus, and the Medical Research Council's report describes some of the results obtained by applying the method to elucidation of the epidemiology of outbreaks of Sonne dysentery in Manchester and London.

It is not certain to what extent the situation as regards Sonne dysentery in Australia differs from that in Britain. Cooper, in his paper on shigellosis in Victoria,[3] reviews briefly the history of shigellosis in Australia, and from this it is evident that the early history of *Sh. sonnei* in Australia followed a pattern similar to that observed in Britain. Its isolation was first reported in Melbourne by S. W. Patterson and F. E. Williams[6] in 1921, but at that time infections due to

[1] "Report of the Ministry of Health for the Year 1958. Part II: On the State of the Public Health", London, H.M. Stationery Office.

[2] *Proc. roy. Soc. Med.*, 1957, 50: 31 (January).

[3] MED. J. AUST., 1958, 2: 770 (December 6).

[4] "Report of the Medical Research Council for the Year 1957-1958", London, H.M. Stationery Office.

[5] *J. clin. Path.*, 1958, 11: 71 (January).

[6] MED. J. AUST., 1921, 1: 460 (June 4).

Sh. flexneri were far commoner, and this was still the case 10 years later. However, in 1951 the position had been reversed, S. Williams[7] in that year reporting *Sh. sonnei* infections to be far more common in New South Wales than those due to *Sh. flexneri*. Cooper himself reports on the examination of specimens submitted to the Public Health Laboratory in Melbourne from 1952 to 1957. With very few exceptions all pathogens isolated belonged either to *Sh. flexneri* Type 2a or to *Sh. sonnei*; *Sh. flexneri* isolations were slightly more frequent, but this may be partly explained by the fact that infections with this organism tend to be more severe. It is perhaps significant that out of 23 family outbreaks investigated, 15 were caused by *Sh. sonnei*. Bearing in mind the recent account of the Mansfield outbreak by G. A. Rickarby *et alii*,[8] there still seems to be little evidence in these figures of the widespread epidemics which were recorded in Britain during the same period.

CURRENT VIRUS RESEARCH

IN 1953 a special number of the *British Medical Bulletin* was published entitled "Viruses in Medicine", giving a thoroughly up to date review of the then known field of virology. After six years the advances made in this aspect of medicine have been so numerous and outstanding that a new number of the Bulletin[1] has been issued with the title "Current Virus Research". Following a brief introduction by Dr. C. H. Andrews of the Medical Research Institute at Mill Hill there are 15 weighty articles beginning with "Virus Genetics" by Sir Macfarlane Burnet of Melbourne and closing with "Myxomatosis" by Professor Frank Fenner of Canberra. It is interesting to note the shift in emphasis from smallpox, mumps, hepatitis and psittacosis to measles, varicella, adenoviruses and trachoma. The use of the developing egg for virus culture was in earlier days responsible for a rapid increment of knowledge, but now the exploitation of tissue culture has given virus research a new and wonderful technique. When it was found that polio virus could grow in cultures of tissues other than neural and produces changes easily visible with low magnification, a great opportunity was offered for active research and innumerable monkeys were reprieved. Specifically human viruses, as those of measles and varicella, can now be grown and studied on human tissue cultures, and the same technique has revealed the existence of adenoviruses, enteroviruses and new respiratory viruses.

When so much important matter is proffered, it is hard to make a selection suitable for a review. Sir Macfarlane Burnet's survey of virus genetics deals with a difficult subject in the manner one expects from this master; much of the work has been carried out with the influenza viruses, and many avenues of future exploration are described. Some of the major conclusions appearing in this Bulletin may be briefly set out. Provided a virus is exposed to antibody before it enters the living cell, immunity can be established; but once it has penetrated the cell wall, it is protected from antibody action. One of the most promising discoveries is that one virus can interfere with the development of another by means of a protein body to which the unattractive name "interferon" has been given, thus indicating that virus infections can be halted by agencies apart from the immunological. Trachoma, almost unknown in Britain but an endemic scourge in undernourished communities, is now shown to have a causative agent belonging to the rickettsial groups midway between the viruses and the bacteria. In diseases which are spread by insect vectors it is convincingly shown that the less virulent are more easily disseminated than those which cause early death of the host. One statement in the poliomyelitis chapter by G. W. A. Dick and D. S. Dane may arouse adverse criticism. The failure of formolized vaccines in America has led certain investigators to suggest that living attenuated strains should be used. This is stoutly opposed by the two authors mentioned. Living viruses have been successfully employed in veterinary medicine to combat rinderpest, distemper and other diseases, but Dick and Dane assert, a little cavalierly, that what is of use in veterinary practice may be a disservice in human medicine. The editor has intervened to point out that smallpox and yellow fever have shown how valuable living vaccines have been in human practice.

Since this comprehensive review was published in 1959 research has been pursued with ever increasing rapidity, so that some of the statements already need amplification—as, for instance, in the discussion of the common cold. A third bulletin may therefore appear in less than six years from the date of this.

[7] MED. J. AUST., 1951, 2:137 (August 4).
[8] MED. J. AUST., 1960, 1:81 (January 16).
[1] *Brit. med. Bull.*, September, 1959.

CARCINOMA OF THE CERVIX.

IN a contributed editorial appearing in *Surgery, Gynecology & Obstetrics*, J. V. Meigs[1] discusses the treatment of carcinoma of the cervix with special reference to another article by G. H. Friedell and J. B. Graham,[2] appearing in the same issue of that journal, in which the authors discuss regional lymph node involvement in small carcinomas of the cervix. Friedell and Graham had conducted a retrospective examination in which they examined the data in 193 cases of Stage I carcinoma of the cervix, in which the primary treatment had been Wertheim hysterectomy and pelvic bilateral lymphadenectomy. These cases were collected from five Massachusetts hospitals and covered the period 1939 to 1955. This investigation was undertaken to test the hypothesis that the fact that the best prognosis is seen in those patients with the smallest lesions is due to the absence of metastases in the regional lymph nodes. Out of their 193 cases, Friedell and Graham found 40 which fulfilled the criteria for inclusion in the series of small carcinomas of the cervix—that is, the lesions measured less than one centimetre in diameter, or the diagnosis of carcinoma was made only after biopsy of a small suspicious lesion. In all these 40 cases, histological examination demonstrated the presence of invasive epidermoid carcinoma, but no lymph nodes were found to contain metastatic carcinoma, and there was no instance of proved metastasis at distant sites. There were six subsequent deaths in this group, but in no case was there evidence of recurrence of the cervical carcinoma; however, it is perhaps of interest that three of the patients in this group died from cancer at other sites.

Meigs acknowledges the importance of Friedell and Graham's investigation, but is anxious that their results should not be misunderstood. He states that he has been distressed by "a small but steady stream of patients coming to our clinics with residual or recurrent cancer following inadequate surgery". He is concerned lest Friedell and Graham's results may be misinterpreted to mean that simple total hysterectomy is the procedure of choice for any invasive cancer of the cervix, no matter how small. He points out that though no metastases were found in the lymph nodes examined, all the patients concerned were treated by radical surgery, and that the parametrial tissues were removed but were not thoroughly investigated, so it is not in fact known whether these areas were involved or not. He asks whether cure was effected in these early cases because lymph channels were not involved or because invaded areas had been carefully extirpated by radical surgery. At the most it is conceded that "the old Wertheim operation, with removal of the paravaginal and paracervical tissues and their lymphatics and a good vaginal cuff" may perhaps be sufficient, without radical lymph node dissection, in the treatment of some very early invasive carcinomas.

[1] *Surg., Gynec. Obstet.*, 1959, 108:616 (May).
[2] *Ibidem*, 1959, 108:513 (May).

Abstracts from Medical Literature.

GYNÆCOLOGY AND OBSTETRICS.

Recent Advances in the Surgery of Infertility.

V. B. Green-Armytage (*J. Obstet. Gynæc. Brit. Emp.*, February, 1959) discusses the changing pattern of pelvic surgery and pelvic pathology in relation to infertility and describes various procedures which have been his special interest. Salpingitis though apparently quickly cured by antibiotics often leaves a legacy of clubbed tubes without palpable abnormality. Infertility due to hydrosalpinx with tubes blocked at their fimbrial ends can now be treated with a 30% success rate in the author's hands. The adherent trumpet ends are opened with sinus forceps and the fimbrial ends are stitched back with four sutures. The tubes are squeezed until empty and 5 to 10 ml. of "Hydrocortisyl" are injected and milked along the length of each tube. Finally the uterus is anteverted by plicating the round ligaments. Rubin tests are performed on the tenth and twentieth post-operative days and immediately after the next two menstrual periods. Tubo-uterine implantation has a success rate of 40% in the author's hands and its technique is now on an established basis. It is employed when the tubes are occluded at or near the cornual and isthmic regions. The condition is usually a sequela of abortion but may occur after retained placenta, prolonged labour or previous ligation of the tubes. The outer two-thirds of these tubes and the ovaries are usually healthy. The author stresses the following points in the operative technique of tubo-uterine implantation: preservation of the blood supply of the tube; special instruments such as a slot-eye needle and a muscle-cutting reamer; fixation of "Polythene" rods to the infundibulo-pelvic ligaments; antibiotic cover; tubal insufflation in two or three months after operation. Endometriosis associated with infertility may have a fairly typical history, but as a palpable entity cannot be diagnosed in more than 3% or 4% of patients. The author recommends the application of the diathermy needle to the multiple "partridge eye" spots found on the pelvic peritoneum. Chocolate cysts are excised rather than fulgurated. A diseased ovary on one side is better removed, together with the tube of the same side, so that all the ova can be produced by the one healthy ovary. Tuberculous infection of the female genital tract gives rise to bilateral salpingitis in 100% of cases and to tuberculous endometritis in 85%. The author considers that operative procedures to improve the chances of pregnancy in this condition are not justifiable. The Stein-Leventhal syndrome is consistently associated with infertility. The author found that surgical treatment of this disease can give a 68% success rate as regards fertility, and at least 90% success from the point of view of menstrual disturbance. X-ray therapy to the hypophysis in patients with amenorrhœa associated with sterility is considered beneficial, but X-ray therapy to the ovaries is best avoided in these cases. The author considers that cervical incompetence plays an important part in the ætiology of habitual abortion. The typical abortion in these cases is usually quick, painless and complete. The diagnosis may be made on the history, feel and appearances of the cervix or on the cervicogram. The author describes his simplified modification of the Shirodkar operation for this condition. No success is reported to follow the operation of utero-ovarian implantation, which is sometimes performed when both tubes have been ablated or destroyed.

The Endometrium in Sterility and Unsuccessful Pregnancy.

E. C. Hughes (*West. J. Surg.*, May–June, 1959) discusses altered function of the endometrium as a hazard in the process of reproduction, possibly resulting in conditions such as sterility, spontaneous abortion, congenital malformation and premature labour. Morphological changes and histochemical and metabolic features of the endometrium in 38 normal patients are compared with the findings in 37 patients who habitually aborted and in 22 patients with histories of frequent premature labours. The endometrium was found to be abnormal in 75% of 200 cases of sterility. The author describes irregularities of the follicular phase and considers them important ætiological factors in sterility and unsuccessful pregnancy. Progestational phase irregularities are more prone to occur in the third and fourth decades of life or in patients who have had repeated pregnancies at short intervals. Metabolism of the endometrium was subnormal, there were diminution of glucose content, decreased alkaline phosphatase and diminished nucleolar activity of glandular cells. Pregnancy may occur under these conditions, but in a high percentage of patients spontaneous abortion, congenital malformation or premature labour will result. Studies on the excretion of chorionic gonadotrophin and pregnanediol in normal patients, in patients who habitually abort, and in patients prone to premature labour are shown graphically. The author concludes that environmental conditions within the uterus are largely responsible for the successful growth and development of the chorion, placenta and embryo.

Combined Radiological and Surgical Treatment of Carcinoma of the Cervix.

Thor Dahle (*Surg. Gynec. Obstet.*, May, 1959) reports a study of 96 patients with Stage I carcinoma of the cervix who were treated by radium therapy followed by radical hysterectomy and lymphadenectomy at the Norwegian Radium Hospital during the period 1954–1956. All operations were performed by the author. The series was a selected one, and most of the patients were young and in relatively good condition. Histological examination showed 88 squamous carcinomas, one adenocarcinoma and seven undifferentiated carcinomas. All patients were primarily treated by intracavitary and vaginal application of radium in a dosage of 6000 to 7200 milligramme-hours. Radical surgery was performed six to eight weeks later. Residual carcinoma was found in the cervix in 16 patients and lymph nodes were involved in 18 patients. In 12 of the latter 18 patients there was no residual cancer in the cervix. There were no operative deaths in the series. Assessment in June, 1958 (after an interval of three to five years), revealed that 12 patients had died, nine of whom had had lymph glands involved at the time of operation. There were no post-operative vesico-vaginal or recto-vaginal fistulæ, but there were four unilateral uretero-vaginal fistulæ. When possible damage to the ureters was sought for by urography six to 12 months after treatment, 22 patients showed abnormalities probably attributable to treatment. Apart from the ureteral fistulæ, there were five patients with hydronephrosis and 11 with slight hydroureter or hydronephrosis. Comparing this series of cases with similar series of patients treated without preliminary radium therapy, the author considers that there is no evidence that radiation therapy destroys metastases in lymph nodes. Moreover, in 12 out of 18 patients with involved lymph nodes there was no residual carcinoma in the cervix, and biopsy of the cervices in these patients would therefore have given a false impression of the prognosis of the disease.

Wertheim Hysterectomy for Endometrial Carcinoma.

L. Parsons and F. Cesare (*Surg. Gynec. Obstet.*, May, 1959) discuss routine methods of treatment of endometrial carcinoma and emphasize our lack of knowledge concerning the manner and degree of spread of growth within the uterine cavity until after the uterus has been removed and closely studied. In view of the possibility of spread of carcinoma beyond the endometrium the authors have employed the radical Wertheim hysterectomy with pelvic node dissection on suitable patients. They report their results in 62 such cases. In 50 of these cases bilateral pelvic lymph node dissection was performed, and in 12 lymphadenectomy was not attempted. The average age of these patients was 57 years. Histologically, there were 52 adenocarcinomas, nine adenoacanthomas and one carcinosarcoma. Fifty-two patients had primary operation, while 10 received previous radiotherapy. Among the 10 patients who received radiation treatment before hysterectomy, six showed residual carcinoma in the surgical specimen. Lymph nodes were involved in four of the 50 patients on whom lymphadenectomy was performed. The carcinoma was limited to the endometrium in 40% of the series. The authors note that those without involvement of the myometrium had a five-year survival rate of 92%, while only 71% of those in whom the myometrium was already involved at the time of operation survived for five years. The authors' operative technique is briefly described and notes are given on pre-operative care and post-operative complications. There was one operative death, and urinary fistulæ developed in five patients after operation. Three patients who developed pelvic recurrences are discussed in detail. The authors consider that the radical surgery described is mandatory in patients with

endometrial carcinoma originating in the lower uterine segment or spreading there from the fundal region, since the lymphatic drainage passes through the paracervical channels in the same manner as epidermoid carcinoma of the cervix. Attempts to assess the extent of endometrial involvement by fractional curettage has not been very successful in their hands. They observe that failure to cure endometrial cancer is usually due to the presence of unsuspected spread of growth.

Trophoblast in the Circulating Blood during Pregnancy.

G. W. WATKINS DOUGLAS *et alii* (*Amer. J. Obstet. Gynec.*, November, 1959) have investigated the presence of trophoblast during pregnancy in circulating blood from the placental site, broad ligament veins, femoral vein, inferior vena cava, ovarian veins and peripheral blood in patients subjected to Cæsarean section; they also investigated the blood of patients undergoing laparotomy for interruption of pregnancy. Trophoblastic cells were found in eight out of the 13 cases in which blood was drawn from the broad ligament vein; similar cells have been found in the peripheral blood of a patient who was 18 weeks pregnant, and in another patient who was 22 weeks pregnant. The frequency of occurrence of trophoblast was much greater in the second trimester, when it was estimated that there was at least one cell per millilitre of blood in the venous return from the uterus. Studies of the peripheral blood, drawn from the ante-cubital vein, have given uniformly negative results in 80 pregnant women. Megakaryocytes are found during pregnancy in samples of vena cava blood and in uterine venous blood. It is suggested by the authors that the presence of these trophoblast cells in the circulating blood of a pregnant woman is immunologically important for the preservation of the pregnancy which must be regarded in the light of a homograft. It is conceivable that the migration of trophoblast cells into the bloodstream throughout gestation is the means by which tolerance is achieved. The difficulty in finding trophoblast in sections of lung taken at autopsy in cases of maternal death suggests that the trophoblast is destroyed in the blood-stream before its arrival at the lungs.

PSYCHIATRY.

Psychiatric Consultation in the General Hospital.

S. K. SCHIFF AND M. L. PILOT (*A.M.A. Arch. gen. Psychiat.*, October, 1959), working in Connecticut, comment that the role of the psychiatric consultant in a general hospital has changed considerably, and has become considerably more than a diagnostic or intermediary service prior to commitment. Their point of view is primarily orientated towards the referring doctor rather than to the patient, and they attempt to examine carefully the manner in which the consultation was requested and the background of each situation. Four case histories are detailed which illustrate the nature of the referring physician's concerns, which have not been made explicit, and how they may operate in the management of the patient. The authors state that this orientation provides an educational function, and that in this framework the psychiatrist does not provide unwanted theoretical, dynamic and diagnostic constructs in the face of practical problems. Rather it provides the referring doctor with the kind of knowledge that comes from working experience.

The Outcome of School Phobia.

A. RODRIGUEZ, M. RODRIGUEZ AND L. EISENBERG (*Amer. J. Psychiat.* December, 1959) report on the academic and social adjustment of 41 children with school phobia approximately three years after they were first seen at the clinic. The authors' findings confirm the hypothesis that this syndrome is a variant of separation anxiety, and the basic issue proved to be leaving home, not going to school. They stress the importance of prompt intervention and their treatment programme of brief psychotherapy, which is centred around returning the child to school as quickly as possible. Therapeutic success was shown to vary inversely with the age of the child and the severity of his psychopathology. School phobia may be the manifestation of a readily reversible situational reaction or of a severely neurotic or even psychotic adjustment. Eighteen children were seen for less than six visits, and a further 14 on less than 12 occasions. Three years later 29 were attending school regularly. The primary factors causing a poor outcome were considered to be schizophrenia, family decompensation, inadequate treatment or medical mismanagement.

Infantile Experience and Adult Behaviour in Animal Subjects.

P. F. D. SEITZ (*Psychosom. Med.*, September-October, 1959) has investigated how the age of separation from the mother during infancy may influence adult behaviour in the cat. Kittens from several litters were divided into three experimental groups: group 1 were separated at two weeks (which causes intense "crying" for a week or more); group 2 were separated when they began lapping milk, usually at six weeks; and group 3 were forced to continue suckling until 12 weeks before being separated from their mothers. All kittens were placed in identical individual cages and life experiences were standardized. At nine months a series of tests of their behaviour were made. These showed that group 1 kittens were the most randomly active, but showed the least goal-directed movements throughout their lives; they were the most anxious in novel situations and were the most persistent, but also the most disorganized in their efforts to obtain food when hungry or frustrated. They were the most aggressive but least successful in feeding competitions, and had the least tendency to share food. Throughout their lives the group 1 animals were more suspicious, fearful and aggressive in their behaviour towards other cats and towards the experimenters. After a feeding frustration test, two of the six group 1 cats developed a chronic wheezing syndrome which had certain similarities to bronchial asthma in humans. The author states that his findings thus confirm the principle that early infantile trauma has persistent effects on adult behaviour lasting throughout life.

Psychosomatic Aspects of Cancer

G. M. PERRIN AND I. R. PIERCE (*Psychosom. Med.*, September-October, 1959) provide a critical review of the literature on the psychological aspects of cancer. Concerning the reports of the slightly higher cancer death rate in psychotic patients in hospital compared with the normal population, they comment that the reason is obscure and may be the inadequacy of the statistics. The psychological reactions and defences of patients to the development of cancer are reported to be similar to those found in neurotics, depression and a sense of guilt being particularly prominent. Some articles have mentioned the development of cancer secondary to emotional trauma, and in others the belief is expressed that cancer appears in patients with specific immature types of personality. One paper concludes that established cancer grows more slowly in less inhibited patients. The authors comment that most of these studies suffer from inadequacy of design, and consequently the findings are open to question. Methods used have been anecdotal, and are based on case histories and interviews, sociological analysis and psychological testing; the present authors stress the necessity for more careful selection, use of control groups, and attention to the nature of the measuring instruments, terminology and statistical analysis.

Statistics, Science and Psychiatry.

J. G. THORPE AND A. A. BAKER (*A.M.A. Arch. gen. Psychiat.*, September, 1959) emphasize that psychiatric disorders are not precise entities, and diagnosis cannot be made with certainty. Clinical trials have other limitations, and the conclusions can refer only to treatments given in a particular trial, as carried out by a particular nursing or medical team. The criteria used to assess improvement must also be considered, and aspects other than statistical significance have to be taken into account (e.g., treatment giving best results may have a higher fatality rate). Psychiatric samples are rarely random or representative, and are better regarded as whole populations, and the authors point out that there is no need to apply elaborate statistical methods to total populations. The concern of science is to establish a body of knowledge by the use of inductive logic and not necessarily by the use of statistics. Statistical evaluation has become necessary to the social scientist because his raw material is infinitely more complex than that of the pure scientist, but this does not mean that statistics make his work more scientific. The authors conclude that much more attention should be paid to the logic of experiments and of statistical analysis than is usually the case. The main functions of statistics in psychiatric articles are often to make the investigations appear more scientific, to assist in having the article published, and to add an air of verisimilitude to their findings.

Points of View.

HYPNOTISM AND SURGERY.

Hypnotism is as old as most civilizations, and has been used in medicine over the centuries, with periodic fluctuations in popularity and esteem. The significance and interpretation of hypnotism and its phenomena have varied with fashion and culture, just as science and art have done. Although the phenomena of hypnotism have been known for centuries, the true essence of hypnotism is still unknown, and there is no entirely satisfactory definition of it. This, however, does not lessen its practical application if commonsense and discretion are used. Many drugs have been employed with benefit long before their mode of action was known.

The British Medical Association subcommittee which reported on "Medical Use of Hypnotism" gave the following tentative description of the hypnotic state without trying to define hypnotism accurately:

> A temporary condition of altered attention in the subject which may be induced by another person and in which a variety of phenomena may appear spontaneously or in response to verbal or other stimuli. These phenomena include alterations in consciousness and memory, increased susceptibility to suggestion, and the production in the subject of responses and ideas unfamiliar to him in his usual state of mind. Further, phenomena such as anæsthesia, paralysis and rigidity of muscles, and vasomotor changes can be produced and removed in the hypnotic state.

The subcommittee decided that:

> In addition to the treatment of psychiatric disabilities, there is a place for hypnotism in the production of anæsthesia or analgesia for surgical and dental operations, and in suitable subjects it is an effective method of relieving pain in childbirth without altering the normal course of labour.

Several incidents in my early years stimulated my later interest. When I was about ten years old, I woke up one night in great distress and fear with what I know now was an attack of asthma. My mother promptly answered my call and said that she would drive everything bad out of my chest so that I could breathe quietly again. Then she started to rub my chest with oil and to repeat reassuring and comforting words, insisting that I would soon sleep and would wake up well. I soon went to sleep, and, as she had said, I was well the next day. So ended my solitary attack of asthma, the deeper implications of which I shall leave to my charitable colleagues among the psychiatrists. I am sure that my mother brought me relief through suggestion and hypnotism, although, as she told me in later years, she knew nothing about hypnotism or psychotherapy.

The next experience came when I was a house surgeon at a London hospital. I was summoned hastily to a ward to see a woman who, the sister said, was having an hysterical fit. I found a young woman shouting loudly and throwing her arms about. I did not really know what to do, but I took one of her arms and raised it high above her head, closed her eyes with my fingers and told her to remain like that until I came back. Twenty minutes later I returned looking more nonchalant than I felt, and found her exactly as I left her. I told her that all was well and that she could open her eyes and move her limbs. She gave no more trouble in hospital; but I did not follow her up as I should have done.

For years these two incidents remained only as vague memories, which came to mind from time to time as a result of casual reading and talking, and of one or two stage performances that I had seen. I did not seriously consider using hypnosis for medical purposes until I read the report of the British Medical Association subcommittee already cited. Not long afterwards I discussed the use of hypnosis with a man who was awaiting pulmonary lobectomy. He was willing to try whether he could be made less afraid of the operation; even the prospect of bronchoscopy frightened him out of proportion. Fortunately he proved to be a good subject for hypnosis, and both of us were pleased with the experiment. He came to operation calmly and had complete amnesia for the operation day; he cooperated well in the post-operative treatment in accordance with my post-hypnotic suggestions. When he required bronchoscopy later, I was able to perform it easily under hypnosis without the aid of sedatives or anæsthesia, and he had no memory of it. From this man's experience I learnt what many others had learnt years before—that suggestion or hypnotism (i) can allay fear and instil confidence, (ii) can supplement or replace sedative drugs and anæsthetics, (iii) can cause amnesia for unpleasant events.

A week later, a woman who was awaiting pulmonary lobectomy said, on the morning of the operation, that she wished I could hypnotize her. I tried, and again was lucky to find a good subject; her experience was similar to that of the man.

Fortified by these two successes, I continued to use hypnotism from time to time for other patients, and I append some brief notes about some of them.

An Italian boy, aged 20 years, was to have a hernioplasty, and he did not want to have general anæsthesia. Under light hypnosis I injected a token quantity of local anæsthetic agent and reinforced this with suggestions of increasing numbness. At no time was he "asleep"; but he bore the operation well, and needed very little sedation afterwards.

A woman, aged 30 years, needed a small skin graft for an old ulcer of the leg. Suggestion of anæsthesia of the donor site was given under hypnosis before and during the operation. She was told that she would feel pressure, but nothing that would upset her. Dr. George Davidson watched for reaction as I cut the graft; except for a slight flinch she seemed to be quite undisturbed. She remained quite still throughout, except when told to raise or turn her leg. Later she said that she knew something was being done, but it did not worry her.

A ship's fireman was admitted to hospital with first and second degree burns of the face, the front of the chest and both arms. He had been given one-quarter of a grain of morphine about an hour before I saw him. He was very restless, and said he could not find a comfortable position. He had had a large meal just before his accident, and it would have been necessary to empty his stomach or wait some hours before a general anæsthetic could be safely given. I explained this to him, and said that the necessary treatment could be done under hypnosis if he was willing. He proved to be a very good subject, and in five minutes he was in a deep trance. He was then taken to the operating theatre, and I stood by his head while my registrar attended to the burns. Except for an occasional movement and groan he did not seem to be aware of what was being done, and he immediately became still and quiet when appropriate suggestions were given. I also gave him post-hypnotic suggestions of comfort and quick convalescence, and I insisted that he would have no fear of future dressings. He accepted all these suggestions so well that he slept until next morning and took all the future dressings as a matter of course. During the whole convalescence he needed only occasional doses of aspirin. He told me, and also nurses, doctors and students independently, that he had no memory of anything from the time that I first spoke to him until he woke up next morning. He left hospital in three weeks, with complete healing and full function.

A man, aged 60 years, complained of constant pain after a thoracoplasty which I had performed several years before. He was very miserable, smoking heavily and taking freely of analgesic drugs. With some misgiving and doubt (which I did not betray to the patient) I decided to try suggestion and hypnosis. The result was very gratifying; he was able to do some light work, he learnt to sleep without drugs and he gave up smoking. Relapse is common with this kind of patient, but he was still well when I last heard from him about a year later.

There has been much solemn talk about the danger of hypnotism. If the surgeon, anæsthetist and general practitioner confine its use to the immediate requirements and do not dabble in hypnotherapy, the psychiatric hazards are few. I would welcome any evidence that mental disturbance is more common after hypnosis than after local or general anæsthesia.

Summary.

1. Hypnotism is a valuable help to the surgeon and anæsthetist; it should also be of value to the physician and general practitioner in suitable cases. Like any other form of treatment, it has its indications and contra-indications, its successes and failures.

2. The risks are small when it is properly used. It is the abuse of hypnotism, especially by lay performers, that is dangerous.

3. There is scope for further observation on and research into the nature of hypnotism and its legitimate uses. The

cases cited are in no way unusual, and are in accord with some of the claims made by medical hypnotists of former days. They appear unusual only to those who are unaware of this earlier work.

Sydney. M. P. SUSMAN.

Reference.

SUBCOMMITTEE OF THE PSYCHOLOGICAL MEDICINE GROUP OF THE BRITISH MEDICAL ASSOCIATION (1955), "Medical Use of Hypnotism", *Brit. med. J.*, 1: Supplement, April 23: 190.

British Medical Association.

NEW SOUTH WALES BRANCH: SCIENTIFIC.

A MEETING of the New South Wales Branch of the British Medical Association was held on May 28, 1959, at the Robert H. Todd Assembly Hall, British Medical Association House, 135 Macquarie Street, Sydney, DR. M. S. ALEXANDER, the President, in the chair.

Osteoporosis.

DR. A. I. RHYDDERCH read a paper entitled "Osteoporosis" (see page 535).

DR. P. J. BENJAMIN read a paper entitled "Osteoporosis" (see page 537).

DR. R. W. THOMPSON congratulated the speakers on their clarity of thought. He said that the papers had made those present realize that bones were living things. Dry bones gave a false idea of bone. There was ceaseless activity in it during life, with bone formation and absorption going on all the time. The greatest activity was tied up with the reproductive period of life. Nature provided a body which operated with efficiency during that period; after that she regarded it as of no consequence with regard to the continuing of the species. Hormones were a *sine qua non* for stopping bones from aging.

DR. NAOMI WING said that the condition unfortunately was all too common. She had in her care at present a woman patient who had been conducting her own lucrative business in the city; a painful back had brought her for treatment, and she was found to have five fish-tail vertebræ and two wedge-shaped ones, obviously fractured. The patient was unable to continue with her business. She had had chronic pyelonephritis for about 15 years, which was apparently causing her calcium imbalance. Dr. Wing said that she also had seen in Chicago the patient mentioned by Dr. Benjamin, and had been horrified at the treatment. There was a great tendency to throw the corticoids about, and everyone should know that people who were highly sensitive to steroids might easily suffer collapse of vertebræ after even small dosage when they were so treated. The information should be more widely known.

DR. B. P. ANDERSON STUART said that radiologists saw osteoporosis mostly of the senile or post-menopausal type. The most that they could do was to report it as osteoporosis to the clinician. Dr. Anderson Stuart said that he had been interested in Dr. Benjamin's remarks about the deficiency being in many cases in the bone matrix and not in calcium absorption. That explained many of the cases in which the blood chemistry was normal. Patients with osteoporosis who were treated improved clinically, but radiologically there was usually no difference. They did not deteriorate further and there were no further fractures or deformities; but even over a period of years repeated X-ray examinations would show no radiological improvement. Dr. Anderson Stuart said that at St. Vincent's Hospital, under the late Dr. Denis Glissan, they had radiologically examined patients with osteoporosis for periods of six years and over, and they had never seen any definite radiological improvement, although there was clinical improvement in most cases.

DR. IAN COLLINS said that he had about six patients suffering from osteoporosis, all in the pre-senile group; all had received hormones, all had felt some subjective improvement, and the treatment of all of them had been unsatisfactory. He was not happy about any of them. Dr. Collins asked the speakers to state the particular hormone combination that they had found satisfactory.

Dr. Rhydderch, in reply to Dr. Thompson, said that in his opinion the patient he had mentioned really had osteomalacia. If she had just had a baby she would certainly not be short of one hormone. Reifenstein had made a point of recording osteoporosis as a clinical entity, not only as a particular radiographic appearance. In reply to Dr. Collins, Dr. Rhydderch said that osteoporosis associated with spontaneous pathological fracture was a very common condition. He believed in a patient's being given any form of light spinal support. In the very chronic cases in which the back ached he believed in the use of braces, because those patients nearly always had spinal deformity. He thought that the pain arose from mechanical disability in the posterior joints of the spine. With regard to hormone therapy, Dr. Rhydderch said that he simply used methyltestosterone and stilbœstrol in small doses. He did not like taking chances with hormones.

Dr. Benjamin, in reply, referred first to the prevalence of osteoporosis. He said that he saw a number of patients, particularly women, with chronic backache of a particular type. The patients rose in the morning perfectly free from pain, which came on later in the day. It became worse in the afternoon, but when they lay down the pain went away. That was in contrast to the pain of rheumatoid arthritis. However, both conditions could be present and often both types of pain occurred together. Dr. Benjamin said that he agreed with Dr. Rhydderch that the patient mentioned by Dr. Thompson had suffered from osteomalacia. That particular idiopathic type of osteoporotic condition occurring after pregnancy was dreadful, because hormones made no difference to it. Referring to treatment, Dr. Benjamin said that he had been using "Methylandrostenediol". Previously he had used methyltestosterone and œstrogen. However, some women patients developed an obvious growth of hair on their face and mammary discomfort, and they did not like that form of treatment. Anderson had watched for some years a series of patients taking synthetic œstrogens. He stated that it was possible to give up to 0·9 mg. of dienœstrol per day for some years. In his series diagnostic curettages had been carried out after three years, and normal endometrium had been found. If larger doses were given, uterine bleeding occurred. If prolonged bleeding or bleeding between menstrual periods occurred, it was necesary to take steps to deal with it. Dr. Benjamin said that one had to treat patients with osteoporosis for a long time. He had had patients receiving treatment with non-virilizing androgens for some years, and they had done very well. He gave a dose of 10 mg. twice a day for three to four months and then a dose of 5 mg. twice a day. It was very difficult to strike the right dose.

Dr. Alexander, from the chair, said that the papers had been very enjoyable, and thanked the speakers on behalf of those present.

Out of the Past.

THE SYDNEY MEDICAL SCHOOL.[1]

[From the *Australasian Medical Gazette*, April, 1899.]

ALREADY New South Wales is overproportioned in the ratio between medical practitioners and the population of the colony. To Sydney graduates in medicine and surgery is accorded the prior claim to the positions of resident medical officers in the leading Metropolitan hospitals, to the detriment of other and possibly more experienced and deserving candidates: in fact, this raw material is deputed to gain experience upon the Sydney maimed and poor. Much tension is produced in Medical circles attached to country hospitals by a claim asserted for similar concessions throughout the colony. Those who originated and fostered the Medical School of Sydney little knew the Frankenstein that they were constructing for the disaster of already existing medical interests in the Medical profession in contributing towards the creation of a soulless fabric calculated to destroy the medical practitioners of New South Wales.

We cannot speak too strongly upon the failure of the professors and lecturers of the Sydney University in contributing to the annals of medical science. We ask after these fifteen or twenty years of so called scientific pursuits in Physiology, Pathology, Anatomy, Medicine and Surgery what useful contributions have been made by the Professional Staff of the University towards the advancement of Medical Science? What have we to show for this eighty thousand pounds spent on the Medical School and the enormous annual expenditure in supplying

[1] From the original in the Mitchell Library, Sydney.

scientific appliances and payment of professors and teachers?

The answer is: nothing whatever—but the overcrowding of the medical profession and the impoverishment of the majority of efficient and hard-working medical practitioners.

Correspondence.

TETANUS PROPHYLAXIS.

Sir: Dr. E. J. Hargreaves (Med. J. Aust., March 5, 1960) purports to argue the value of anti-tetanus serum by reporting that a single dose of tetanus toxoid is an unsatisfactory prophylaxis against tetanus.

The truth is surely that neither therapy will provide sure protection. The significant difference in the two procedures lies in the fact that one, A.T.S., carries a very high morbidity rate and a significant mortality, whereas the other is safe and, moreover, is the first stage of a procedure which when completed will provide prolonged protection. The A.T.S. reaction is an iatrogenic condition, which is far more common and occasionally just as severe as the disease which prompts us to inflict it.

By adopting the approach suggested by Dr. Walsh (Med. J. Aust., January 23, 1960) and Dr. K. D. Murray (Med. J. Aust., September 23, 1959) we will the more rapidly have a fully immunized population, and so be rid of not one disease but two—tetanus and A.T.S. anaphylaxis.

Yours, etc.,

M. E. Whisson.

75 Mason Street,
Hawthorn, Victoria.
March 11, 1960.

MEDICAL RESEARCH IN AUSTRALIA.

Sir: The recent discussion on the financial and directorial problems of medical research in Australia gives me a peg on which to hang what I hope is constructive criticism of the purely clinical aspects. My criticism stems from my experience in a research department in a teaching hospital overseas, but I know I am not alone in holding the opinions I am now airing.

First, while all medical men pay lip service to the value of clinical investigations in general, few take the trouble to ensure that they are possible. By clinical investigations I mean in particular retrospective surveys of the value of various forms of treatment, ætiological factors, methods of investigation of individual patients, etc. This particularly applies to cases hospitalized in the teaching centres for specialized treatment or even for simpler forms of therapy. General practitioners usually have neither the time nor the qualifications to record all the observations or analyse the results required in a research problem.

Let me amplify this by saying that the first essential in research is the collection of facts. If no one collects them routinely in every case, no one can deduce anything from their correlation. Once findings are made, they must be recorded in easily assimilable form. They are of little use in a clinician's head unrelated to patient, disease or treatment. The recording itself does not have to be on special complicated pro-formæ, which are of little practical value even in prospective studies for which they have been designed, unless the investigator himself completes them from direct observation. A routine history and a full examination, including, in their chronological order, the results of radiological, biochemical, pathological and other special investigations, is all that is necessary initially. Subsequent information can be confined to the disease in question and its related manifestations. To clutter up a case sheet with useless information unrelated to the problem is quite futile, as no one has the time to sift all the possible investigations of every patient. In this respect routine investigations should be regularly reviewed to see if they provide useful information. If they do not, time and money should not be wasted on their performance.

On the front sheet, easily available for both the clinician seeing the patient and the investigator, should be the personal details of each case. Basic facts are occasionally missed: a wrong name, no age, an age that does not correspond to the date of birth is quite common; an out-of-date address; I have seen one in which the sex was impossible to determine on subsequent reading; the patient's general practitioner and any consultant referring the case. All these should be recorded if follow-up information is to be obtained after the patient has been discharged or failed to attend. The diagnosis and the stage of the disease should be given a prominent place and never left blank. Changes in diagnosis should be recorded in such a fashion that the previous diagnosis is legible. Changes in staging should never be made subsequent to the patient's first attendance. Then should follow a clear, dated history including investigations done previously with their dates. Dating events saves the confusion which can arise with "a month before" and often leads to greater accuracy in the patient's memory of events. The clinical examination and the dated performance of special procedures—not the date of the report, as this can be confusing, especially when several biopsies are taken from different sites—should be appended. As to treatment, the date of the first definitive treatment must be recorded, as it is to this date that survival rates refer. A biopsy or laparotomy for investigation is not a definitive treatment. If no definitive treatment is offered, the date of decision not to do so becomes the date from which survival counts, and it is essential that no case sheet for which a diagnosis has been made should be without a date from which a survival can be calculated. A clear statement as to whether the treatment is to be radical or palliative, to include other measures or stand alone, is a most useful piece of information.

I do not think this is terribly difficult or tedious. The bare facts I have enumerated are required, not only for research, but for the information of anyone who sees the case in the absence of the first consultant. To leave a sheet or even to refer a patient as "carcinoma breast—mastectomy" is to condemn that patient to inadequate treatment in the event of recurrence, and to invalidate any comprehensive survey of a centre's results in carcinoma of the breast, as all cases should be included.

Secondly, Australia has few, if any, specialists; plenty, if not more than enough, consultants, but no specialists. Medicine has now reached the point where one's attention must be focused on a very small segment of the branch one has embarked on, to keep up with all the pertinent developments. This is reflected in the increasing number of publications devoted to one aspect of medicine or surgery and the increasing popularity of "abstract" types of periodicals. For the occasional problem case the consultant with the widest experience of all types of cases may make the correct diagnosis. He will rarely be able to prescribe the best form of treatment, and almost never be able to carry out optimum surgery or other forms of physical therapy under optimum conditions with well-trained assistants. More pertinent to the subject of this letter, he will be unable to contribute materially to clinical research. True "specialization" permits the collection of a statistically significant series of cases in a reasonable time, the evaluation of old methods of treatment and the initiation of new ones. The greatest contribution to medicine comes from the improvement of therapy for common conditions or, better, their prevention, not from the academic discussion of esoteric conditions for which diligent searches of unfamiliar literature are required.

Thirdly, adequate follow-up studies of public patients are the exception rather than the rule. One can scarcely blame the consultant for this, as his honorary post is often a financial liability. Time spent away from private practice is, to him, better spent on gaining experience on new patients rather than seeing old ones treated several years ago with either complete success or complete failure. Nothing can often be done for either, but very little inquiry is initiated into the reasons for failure. Careful analysis of one's cases can often provide a more rewarding experience than initiating more of the same therapy on more patients. For an independent investigator requesting access to case records rebuff is not uncommon, and in the event of cooperation, a disappointing yield of information is usual.

In defence, consultants are going to say that the recording of public patients' cases is the business of the resident. One can scarcely blame the new graduate for his crimes of omission when he has had no training, either before or after his final exams, in this subject. It is only when one attempts the analysis of a series of histories that one realizes how important accurate recording is. To my second point, the merits of the older practitioners will be flaunted: the surgeon, who could turn, bloody but unbowed, from a Wertheim, to undertake the

removal of an astrocytoma, closely followed by an œsophagectomy; the physician, whose patients revolved through his rooms in a succession of blood dyscrasias, cardiological defects, endocrinal upsets and psychosomatic disorders. I certainly do not deny their merit and, indeed, have the greatest admiration for their versatility, which must have been a great asset in isolated situations. But now that modern transport has shrunk distances and opened up inaccessible districts, there is little excuse, on this account, for attempting the difficult under impossible conditions or the unfamiliar with an inexperienced staff. It is only by restricting the conditions one treats to a small section of the vast body of ill health that one becomes familiar with what, to others, is uncommon. It is only by gathering a team of staff around one who know their job, and exactly how each contributes in the whole management of the patient, that one delivers the service which was promised on graduation. It is therefore implicit that conditions outside one's own field are referred, with full autonomy, to the specialist or department concerned. There is no disgrace in admitting inadequacy outside one's chosen field.

I must make it clear that I am not denigrating the many individual case reports and small series which grace your columns; but it is perhaps significant that the reputation of medical research in Australia is upheld overseas mainly by the Walter and Eliza Hall laboratory. The fact remains that significant contributions can only be made by large numbers of accurately examined and carefully recorded cases.

Yours, etc.,

65 Union Road, Surrey Hills, Melbourne, Victoria. T. F. SANDEMAN.
March 10, 1960.

CANCER, A DISEASE OF THE NERVOUS SYSTEM.

SIR: I have no desire to cross swords with Dr. B. Haynes or Dr. R. Amati in relation to autonomic dyspraxia. But suffice to say that autonomic dyspraxia should not be brushed easily aside, in that I beg to offer the opinion that there is no one single cause of cancer. Whether autonomic dyspraxia is due to emotional, metabolic or some other dysfunction I do not know. Methinks the answer will come from him who can tell us what came first, the chicken or the egg. It is often overlooked that you must get dysfunction before you get disease.

Yours, etc.,

241 Oxford Street, Bondi Junction, N.S.W. KENNETH ADDISON.
March 14, 1960.

PROPORTIONAL REPRESENTATION ON THE N.S.W. BRANCH COUNCIL.

SIR: Discussing "General Pharmaceutical Benefits" in a letter to THE MEDICAL JOURNAL OF AUSTRALIA of February 20, Dr. C. Jaede worked round to the above subject. I myself refer only to the above heading primarily, and hence indirectly to the question of urgent decisions to be made by the profession; of these the question of General Pharmaceutical Benefits is but one example, though perhaps a forerunner of others.

Firstly, Dr. Jaede usefully reminds us what is known to all (and known as a farce to many), that all members of the Association are entitled to vote for the election of women candidates, Civil Service candidates and country local associations; or, put another way, these elected members are no more elected by their own groups than the lottery money is ear-marked for hospitals. A comprehensive scheme was prepared years ago (and should still be in possession of Council) providing for true representation on Council; machinery was called upon which it was hoped would allow a favourable opinion of the Association to become effective; but at the earliest stages the plan was watered down to near futility, and still every member receives a voting card containing many names of members whom he really knows poorly, if at all—and still no group of members elects its own representative. Until this situation is altered, one must challenge the oft-made claim that our representation is properly democratic!

Secondly, on the question of rapid decisions, I would point out the advantage in this regard of proportional representation. It should be clear that on a message to the secretary of each group having a representative on Council, each such group could have a meeting over a single week-end if necessary—advise its representatives of the feeling and wishes of the group; and Council could then meet immediately and record the consolidated votes of members of the Association, each single member of which would have a vote equal to any other.

I urge that all local associations and special groups should take this matter up immediately, or at least at the first sign of the next crisis.

Yours, etc.,

143 Macquarie Street, Sydney. C. C. MCKELLAR.
March 16, 1960.

THE GENERAL PRACTITIONER AND HIS WAITING ROOM.

SIR: It is most unfortunate that the patient accommodation at so many out of town and country general practitioners' surgeries has not kept pace with the doctor's greater skills and wider knowledge. With deplorably few exceptions, these "waiting rooms" are stuffy, cramped and hot or cold according to the season. Many have remained unchanged since the turn of the last century, except for the removal of the aspidistra so that one additional chair might be wedged in.

But, most deplorable of all, is the complete lack of privacy in the consulting room. The waiting patients sit literally knee to knee, in a silence in which it is quite impossible not to overhear every word exchanged between doctor and patient. This almost universal laxity on the part of the out-of-town doctor is the more reprehensible since medical ethics have always been regarded as very strict on this point.

Ethics apart, nothing could be more objectionable than to know one's most intimate symptoms are being broadcast to all those reluctantly awaiting their turn for this indignity. Should not the patient, waiting sometimes for an hour in frequently miserable conditions, be entitled to expect some standard of comfort and particularly privacy just as he expects a standard of competency in his doctor?

Yours, etc.,

New South Wales, February 13, 1960. PATIENT.

GENERAL PHARMACEUTICAL BENEFITS.

SIR: Having barely tolerated the first three weeks of the new National Health Scheme system, I now hear that a new list of regulations and so-called benefits are to be foisted upon us. And to add to our overwhelming clerical duties, the universally used rubber date stamp is to be banned. How petty can petty official minds get!

Surely the profession must vote a resounding "no" to the recent B.M.A. plebiscite. There can be no other body, professional or unionist, who would tolerate such pettifogging nonsense from an allegedly responsible Government.

Yours, etc.,

Sydney. March 19, 1960. IRATE SUBURBAN PRACTITIONER.

SIR: In his *De Senectute*, Cicero points out that growing old can have its compensations. So it is that, as I approach the seventy-year mark and am now in semi-retirement, I can look on the bureaucratic inroads on the status of our profession with a certain amount of detachment, if not with equanimity (*pace* Osler).

As one who took part in the 1948 struggle for independence, I cannot help feeling that our victory against that attack on our freedom was but a temporary respite. Just prior to 1st instant I received the new plastic-covered 135 page edition of "Notes for Medical Practitioners" from the Commonwealth Department of Health. An introductory sheet remarks among other things "It is essential . . . that the Book be carefully studied", pointing out that an amendment would be issued at a later date. This later

date occurred three days later, when a further 17 pages arrived. The importance of some of these amendments may be realized when some 20 lines are devoted to details about—yes, indeed, aspirin!

Judging by past experience, we may now look forward every few weeks to receiving further lists of amendments of more or less importance. One can imagine what an army of civil servants must be occupied in compiling and dispatching this never-ending stream of documents.

Is the medical profession allowing itself to be overwhelmed by the Welfare State? The plebiscite now being held in this State should give some indication of the views of present-day doctors, unless apathy deters them from registering their votes.

Yours, etc.,

19 Beauty Point Road,
Mosman, N.S.W.
March 15, 1960.

A. W. J. BULTEAU.

SIR: Are we doctors or morons? What has happened to the pride in our profession of which we were so zealous a few years ago? The new National Health Service scheme is bureaucracy at its very worst. We are a profession of duplicates and triplicates, restricted drugs, pensioner only, children only, repeated once or umpteen times, etc.

How was this scheme ever foisted on a once proud profession? Surely our advisers (the B.M.A.) could not in conscience approve of this travesty of medicine. The politicians who suggested this scheme should themselves interview a psychiatrist and beg for some "Largactil" on the N.H.S.—only to be refused. They may be given 12 "Carbrital" capsules, to help make them sleep, at 5s. per 12, and by the time they have taken 100 they would have paid to the chemist 45s. The price for 100 dispensed on a private script would have been 31s. 6d. What price glory—or should I say, N.H.S.?

We as doctors are fully aware of the hoax of this scheme as far as the general public is concerned. We are also fully aware of the amount of stationery and carbon paper we all use. Let us unite and tell the politicians that the scheme is dishonest, foolish and we refuse to cooperate with it any longer.

Yours, etc.,

Otho Street,
Inverell,
New South Wales.
March 16, 1960.

F. C. BYRNES.

SIR: Dr. Poolman (MED. J. AUST., March 19, 1960, page 475), and indeed all members of the Association, should be informed that, prior to the meeting of the Federal Council, the Council of the New South Wales Branch took pains to obtain the opinion of the profession in New South Wales. This was done through the various local associations. The answer was an unequivocal "No". I do not know whether the representatives of other Branches were as well informed on professional opinion in their States as were the representatives of the N.S.W. Branch in theirs.

Yours, etc.,

235 Macquarie Street,
Sydney.
Undated.

W. L. CALOV.

ACCIDENTS AND SICK PAY.

SIR: A patient of mine fractured his finger whilst playing cricket. I supplied him with a medical certificate to this effect and was surprised to learn that his employer had refused to grant him sick pay. According to the strict letter of the law the company concerned may be correct, because the award under which this employee works (the Metal Trades Award) states that sick pay shall be granted if "in the medical practitioner's opinion the employee was unable to attend for duty on account of personal illness".

However, the company concerned in their employees' manual have placed their own interpretation upon this award. In this manual the following statement occurs: "The Federal Metal Trades Award conditions cover sick pay and not injury by accident pay." Apparently the basis for this interpretation was a test case some time ago. If this is so, then it would seem unlikely that the Union had expert medical witnesses to support their argument.

How an accident could not be considered medically to be a personal illness I fail to understand. Is a cerebrovascular accident, an accident? Is cirrhosis of the liver due to excessive consumption of alcohol a personal illness? In what category would tetanus be placed? Here we have trauma of some kind plus the presence of the tetanus bacillus.

In this particular case the company concerned are practising a big bluff, and because of their power they are able to dictate the end result.

Prospective employees of the company to which I have referred are subjected to a preemployment medical examination. Unfortunately this examination is not for the purposes of placing the person in suitable employment, but to determine whether or not he or she shall be employed at all. This policy is reminiscent of the days of slavery, when the slave owners would palpate the muscles of the slaves to determine whether they were fit to purchase. Fortunately for Australia, this is not a widespread practice in industry.

If this were the case, then the ailing members of our society would carry the additional burden of unemployment.

Yours, etc.,

366 Church Street,
Richmond, E.1,
Victoria.
March 12, 1960.

BARRY E. CHRISTOPHERS.

"TOFRANIL."

SIR: The results obtained by the authors of the two papers regarding the efficacy of "Tofranil" (imipramine hydrochloride) in psychiatric practice, with particular reference to depressive states, are of somewhat limited interest. The findings in both cases must be evaluated with very great care before they can be accepted at their face value.

It is true that Stoller describes his investigation as a "pilot study", whilst MacLean *et alii* qualify theirs as a "preliminary report". But when will workers in the field of drug evaluation learn the lesson that such trials are virtually useless unless some technique such as a "double-blind" is used? (Modell,[1] Marley.[2]) Wolf and Pinsky[3] put the matter cogently when they write:

> Periodically it is observed that the introduction of a new drug is followed by a cluster of favourable reports of its therapeutic value. Later it is often discovered (but not always published) that the agent has no appreciable therapeutic action . . . the good results [may really have been] attributable not to pharmacological properties of the agent but to very real and often powerful placebo effects.

Such reports as those by Stoller and MacLean *et alii* would seem to be the end result of considerable, but relatively unprofitable, industry. A well-designed trial using smaller numbers than their combined 132 patients would have been a much more scientific and valuable contribution and would not have been any more time-consuming. It has to be recognized that one of the earliest papers (Kuhn[4]) recommending the use of "Tofranil" in depressive states was published in 1957, and therefore all trials after the initial reports should be adequately controlled if they are to be of value to the clinician, who wishes to know how effective a certain drug is from the pharmacological point of view.

The results of Sloane *et alii*[5] are of interest in this respect. A beneficial result in the treatment of depression with "Tofranil" was noted in an uncontrolled trial, but a short duration "double-blind" trial using small numbers demonstrated no significant difference between the drug and placebo. The latter findings cannot be considered to represent a total indictment as to the efficacy of the drug, but they are in accord with results obtained from an investigation of my own using a similar technique (in preparation).

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[1] "The Relief of Symptoms", 1955, Saunders, Philadelphia, 88.
[2] *J. ment. Sci.*, 1959, 105: 19.
[3] *J. Amer. med. Ass.*, 1954, 155: 339.
[4] *Schweiz. med. Wschr.*, 1957, 87: 1135.
[5] *Canad. med. Ass. J.*, 1959, 80: 540.

The enthusiasm with which tranquillizers and other new drugs are initially hailed would seem to be so very often ephemeral. The controlled trial by Raymond *et alii*[1] using amylobarbitone, a placebo and four other "tranquillizers" produced results that should be more than an adequate warning to all who tend to hail each new pharmacological candidate as the "drug of choice", or all who carry out clinical trials without using some form of control.

Yours, etc.,

4 Adamson Street,
Heidelberg,
Victoria.
March 20, 1960.

ALLEN A. BARTHOLOMEW.

Post-Graduate Work.

THE POST-GRADUATE COMMITTEE IN MEDICINE IN THE UNIVERSITY OF SYDNEY.

GENERAL REVISION COURSE.

THE Post-Graduate Committee in Medicine in the University of Sydney announces that the annual general revision course will be held in Sydney for two weeks beginning on May 9, 1960. As in previous courses, the main emphasis is on therapeutics, and in addition the programme, as in former years, is a comprehensive survey of modern trends in diagnosis and treatment of special value to general practitioners. The programme is as follows:

Monday, May 9, at the I.C.I. Theatrette, 69 Macquarie Street, Sydney: 9.15 a.m., registration; 9.45 a.m., welcome and opening of the course by Sir Charles Bickerton Blackburn, K.C.M.G., Chancellor of the University of Sydney; 10 a.m., review of course by Dr. V. M. Coppleson, Honorary Director; 10.45 a.m., "Changing Trends in Medicine", Dr. T. M. Greenaway; 11.45 a.m., "Essentials in Head Injuries", Dr. I. Douglas Miller; 2.15 p.m., symposium on the anæmias: "Advances in Diagnosis and Treatment", the chairman, Professor C. R. B. Blackburn; "Pernicious Anæmia and other Macrocytic Anæmias", Dr. H. Kronenberg; "Iron Deficiency", Dr. P. Lamond; "Anæmia, Infection and Malignant Disease", Professor C. R. B. Blackburn; "Anæmias in Pregnancy", Dr. T. I. Robertson; discussion.

Tuesday, May 10, at the I.C.I. Theatrette, 69 Macquarie Street, Sydney: symposium on "Common Skin Diseases in General Practice", chairman, Dr. J. C. Belisario; 9.15 a.m., "The Use of Griseofulvin in Fungous Diseases", Dr. M. T. Havyatt; 9.35 a.m., "The Treatment of Plantar Warts", Dr. M. B. Lewis; 9.50 a.m., "Stasis Ulcers and Dermatitis", Dr. L. G. Abbott; 10.35 a.m., "Sunlight and Skin', Dr. R. B. Perkins; 10.55 a.m., "The Diagnosis of Industrial Dermatitis", Dr. B. S. Mackie; 11:15 a.m., discussion; 11.55 a.m., "Treatment of Tetanus", Dr. Brian Dwyer; 12.25 p.m., "Immunization Procedures for Children", Dr. E. S. A. Meyers; 2.15 p.m., "Gout", Dr. Selwyn Nelson; 3.45 p.m., "Observations on Public Health", Professor Sir Edward Ford.

Wednesday, May 11, at the Stawell Hall, 145 Macquarie Street, Sydney: panel discussion on therapeutics, chairman, Sir William Morrow; 9.15 a.m., "Anticoagulant Therapy, Including Long-Term Therapy", Dr. J. Sevier; 9.30 a.m., "Diabetic Drugs", Dr. F. Hales Wilson; 9.45 a.m., "Use and Abuse of Tranquillizers", Professor W. H. Trethowan; 10 a.m., "Indications for a Choice of Diuretics", Dr. Ralph Reader; 10.15 a.m., "Mucolytic Agents in Respiratory Diseases", Dr. Maurice Joseph; 10.50 a.m., "Antibiotics", Dr. J. E. Hassall; 11.05 a.m., discussion. The afternoon has been kept free for private arrangements and other specially arranged activities. A choice is offered to members to visit the following: 2.30 p.m., Isotope Laboratory, St. Vincent's Hospital, Darlinghurst; or the Australian Atomic Energy Commission Research Establishment, Lucas Heights, the latter being limited to 24 (special application forms are available from the Committee). 8.15 p.m., "Coronary Occlusion", Professor John McMichael, M.D., F.R.C.P., F.R.S., Sims Commonwealth Travelling Professor for 1960.

Thursday, May 12, at the I.C.I. Theatrette, 69 Macquarie Street, Sydney: 9.15 a.m., "Endocrine Problems in General Practice", Dr. K. S. Harrison; 10.45 a.m., "The Treatment of Acute Alcoholism", Dr. S. J. Minogue; 11.45 a.m., "The Problem Child", Dr. Alan Jennings.

[1] *Brit. med. J.*, 1957, 2: 63.

Thursday, May 12, at Broughton Hall Psychiatric Clinic, Leichhardt: 2.15 p.m., demonstration of psychiatric problems by Professor W. H. Trethowan and the staff.

Friday, May 13, at the I.C.I. Theatrette, 69 Macquarie Street, Sydney: 9.15 a.m., question session on medical subjects; chairman, Dr. T. M. Greenaway; panel, Dr. Richmond Jeremy, Dr. J. Kempson Maddox, Dr. James Isbister, Dr. George V. Hall, Dr. G. E. Bauer.

Saturday, May 14, at the Red Cross Blood Transfusion Centre, 1 York Street, Sydney: 9.15 a.m., demonstration of blood grouping, Rh testing and blood transfusion techniques, Dr. Hugh K. Ward and Dr. R. J. Walsh.

Monday, May 16, at the I.C.I. Theatrette, 69 Macquarie Street, Sydney: symposium, "The Complicated Obstetric Case', chairman, Professor Bruce T. Mayes; 9.15 a.m., "Modern Views of Hyaline Membrane: Hæmolytic Disease", Dr. Ian Cope; 10 a.m., "Conditions Causing Sudden Maternal Collapse in Labour", Dr. Stanley D. Meares; 11.15 a.m., "Improved Induction of Labour", Associate Professor R. P. Shearman; 12 noon, "Any Questions?"; symposium, "Gynæcological Problems in General Practice", chairman, Dr. George G. Stening; 2.15 p.m., "Vaginal Discharge", Dr. R. H. Macdonald; 2.45 p.m., "Fibroids from the General Practitioner's Point of View", Dr. C. V. Salisbury; 3.35 p.m., "Recurrent Urinary Infections", (*a*) Dr. H. H. Pearson, 3.55 p.m., (*b*) Dr. F. N. Chenhall; 4.15 p.m., discussion.

Tuesday, May 17, at the Main Lecture Theatre, Royal Alexandra Hospital for Children, Camperdown: 9.15 a.m., "Cyanosis of the Newborn", Dr. R. H. Vines; 10.30 a.m., "Otorrhœa", Dr. O. J. Davies; 11.30 a.m., "Urinary Tract Infection in Childhood", Dr. John McDonald; 2.15 p.m., "Osteomyelitis in Childhood", Dr. J. Steigrad; 3.30 p.m., "Pædiatric Emergencies", Dr. W. Grigor; 4.30 p.m., question time, Dr. D. G. Hamilton, Dr. D. Cohen, Dr. W. Grigor.

Tuesday, May 17, at the Stawell Hall, 145 Macquarie Street, Sydney: 8.15 p.m., symposium, "What s New in Drugs and Therapeutics", chairman, Dr. C. G. McDonald; "Darenthin and Modern Anti-Hypertensive Drugs", Dr. F. L. Rothwell; "The Treatment of Ulcerative Colitis", Dr. A. P. Skyring; "The Drug Treatment of Epilepsy", Dr. W. J. Burke; "The Rationale of Steroid Therapy", Professor C. R. B. Blackburn; question time.

Wednesday, May 18, at the I.C.I. Theatrette, 69 Macquarie Street, Sydney: 9.15 a.m., "Ophthalmology in General Practice", Dr. N. M. Macindoe; symposium, "Anæsthetics", chairman, Dr. L. T. Shea; 10.45 a.m., "Common Anæsthetic Difficulties', Dr. Brian Crawshaw; 11.10 a.m., "Premedication", Dr. Brian Pollard; 11.35 a.m., "Obstetric Anæsthesia", Dr. Janet Bowen; 12 noon, discussion; 2.15 p.m., "Ear, Nose and Throat in General Practice", Dr. Volney Bulteau; 3.45 p.m., "Cardio-Vascular Collapse in the Operating Theatre" (with film), Dr. Bruce Clifton and Dr. Rowan Nicks.

Thursday, May 19, at the I.C.I. Theatrette, 69 Macquarie Street, Sydney: 9.15 a.m., practical demonstration, "Allergic Investigation, Treatment and Causation", speakers, Dr. D. O. Cross, Dr. Peter Waugh and Dr. Basil Williams; symposium, "Orthopædic Problems in General Practice", chairman, Dr. N. H. Morgan; 10.45 a.m., "Metatarsalgia: Flat Feet", Dr. N. H. Morgan; 11.05 a.m., "Backache", Dr. W. D. Sturrock; 11.25 a.m., "Disabilities of the Knee", Dr. W. A. Hugh Smith; 11.45 a.m., "Sub-Deltoid Bursitis", Dr. A. I. Rhydderch; 12.05 p.m., "Calcification about the Shoulder Joint", Dr. A. R. Hamilton; 12.25 p.m., discussion; 2.15 p.m., symposium, "Surgical Problems in General Practice", chairman, Dr. F. W. Niesche; "Gastro-Duodenal Surgical Problems in General Practice", Dr. C. E. Winston; 2.35 p.m., "Choice of Operation in Some Common Abdominal Emergencies", Dr. Norman Wyndham; 2.55 p.m., "Gall-Bladder', Dr. E. G. MacMahon; 3.45 p.m., "Management of Hernia in Infants", Dr. Eric Goulston; 4.05 p.m., "Surgery of the Breast", Dr. J. M. Yeates; 4.25 p.m., discussion.

Friday, May 20, at the I.C.I. Theatrette, 69 Macquarie Street, Sydney: 9.15 a.m., panel discussion, "Problems in Medical Practice", moderator, the Honorary Director, Dr. V. M. Coppleson; specialist panel, Dr. S. H. Lovell, Dr. A. E. McGuinness, Dr. Angus Murray, Dr. Frank Ritchie; course panel, six members of the course, who will be chosen to act as monitors; 11.45 a.m., discussion groups; 12.30 p.m., conclusion of course.

Social Activities.

Social activities arranged during the course include the following. On Tuesday, May 10, at 5.30 p.m., a cocktail party will be held in the ballroom of the Australia Hotel. The Post-Graduate Golf Cup Competition will be played at the Royal Sydney Golf Club, Rose Bay, Sydney, on

Friday, May 13, from 12.30 p.m. The Brydon Cup will be awarded to the country member attending the general revision course who obtains the best score.

Annual Post-Graduate Oration.

The thirteenth Annual Post-Graduate Oration will be given by Dr. George Wilcocks on "The Sydney Hospital Group at the Turn of the Century", on Thursday, May 19, 1960, at 8.15 p.m., in the Great Hall of the University of Sydney.

Financial Assistance to Practising Doctors in Isolated or Remote Areas of Australia.

The Post-Graduate Committee has set aside a sum made available by the Post-Graduate Medical Foundation to assist practising doctors in isolated or remote areas in Australia towards payment of fares and fees in attending the general revision course in 1960. Grants up to £50 per person will be made. Early application is essential.

Fees and Method of Enrolment.

The fees for attendance are as follows: full course, twelve guineas; mornings or afternoons only, six guineas; one week only, six guineas. Early application, enclosing remittance, should be made to the Course Secretary, The Post-Graduate Committee in Medicine, 131 Macquarie Street, Sydney. Telephones: BU 4497-8. Telegraphic address: "Postgrad Sydney". Fees and travelling expenses for this course are taxation deductions for those who are at present in practice. When such deductions are claimed, "Taxation—File No. AF/1865" should be quoted.

ROYAL PRINCE ALFRED HOSPITAL: EAR, NOSE AND THROAT DEPARTMENT.

Seminar Programme, 1960.

THE staff of the ear, nose and throat department of the Royal Prince Alfred Hospital will conduct a seminar on the second Saturday of every month at 8 a.m. in the Scot Skirving Lecture Theatre. The main speaker will not exceed forty minutes, and there will be a discussion at the conclusion of his remarks. All medical practitioners and clinical students are invited to attend.

At the next seminar, to be held on April 2, 1960, Dr. J. H. Lancken will speak on "Malignant Tumours of the Larynx: The Results of Treatment in the Past".

Notes and News.

A Dinner in Honour of Professor J. McMichael.

A dinner at Sydney in honour of Professor J. McMichael is being planned by ex-members of the medical staff of Hammersmith Hospital. Any former Hammersmith residents who are interested are asked to get into touch with either of the following: Dr. G. E. Bauer, telephone BW 9031; Dr. P. N. Francis, telephone BW 1291, Sydney Hospital.

First International Symposium of Cybernetic Medicine.

The International Society of Cybernetic Medicine announces that the first International Symposium of Cybernetic Medicine will be held at Naples from October 2 to 4, 1960, under the presidency of Professor Aldo Masturzo, of the University of Naples. The general theme of the symposium will be "The Introduction of Cybernetic Methods in Modern Medicine". The official speakers will be: Professor Norbert Wiener, Director of the Department of Mathematics, Massachusetts Institute of Technology; Professor Paul Nayrac, Director of the Neuropsychiatric Department, University of Lille; Professor S. T. Bok, Director of the Institute of Brain Research, University of Amsterdam; Dr. Giuseppe Foddis (engineer), Director of S.E.T., Naples; Professor Minoru Kono, Director of the Institute of Medical Research, Tokyo. The complete list of speakers and prospective changes in schedule will appear in the final programme. A number of excursions and other attractions are being arranged in connexion with the Congress. Further information may be obtained from Professor Renato Vinciguerra, Secretary, S.I.M.C., Via Roma 348, Naples, Italy, to whom applications for registration, accompanied by the fee of $10 and the titles of proposed communications, should be sent by June 30, 1960.

Sixth International Congress of Internal Medicine.

The sixth International Congress of Internal Medicine, organized by the International Society of Internal Medicine (the president of which is Sir Russell Brain), will be held from August 24 to 27, 1960, at Basle, Switzerland. The two principal subjects of the Congress are œdema and enzyme regulation. In addition there will be a number of panel discussion on other subjects. Seventy authorities in the field of internal medicine will take part in the main scientific programme. The official languages are German, French and English, and there will be simultaneous translation for the principal lectures. The President of the Congress is Professor A. Gigon, of Basle, and the Secretary is Professor H. Ludwig, of Basle, from whom programmes and registration forms may be obtained. Applications for registration should if possible reach the Secretary by April 30, 1960. The address is as follows: Steinentorstrasse 13, Basle 10, Switzerland.

Medical Research Council of the Privy Council: Nathan Trust Research Fellowship.

The Medical Research Council of the Privy Council invites applications for a research fellowship provided through the generosity of the Nathan Trust. This appointment is being made under the auspices of a special committee set up by the Council for the evaluation of different forms of therapy in bone sarcoma. Candidates should be clinically experienced British medical graduates, who should preferably have some knowledge of research methods in clinical medicine, surgery, pathology or radiology, and should be willing to engage in this investigation for at least two or possibly three years, if the progress of the research should so require.

The fellowship is tenable in the United Kingdom, and will provide a salary of £1500 to £2000 *per annum* according to age and experience, with superannuation provision in addition; the appointment will be made for one year in the first instance, but is renewable for up to three years subject to satisfactory progress. Applications, giving a full *curriculum vitæ*, a list of publications and the names of two referees (two signed testimonials in the case of candidates overseas) should be sent to the Secretary, Medical Research Council of the Privy Council, 38 Old Queen Street, Westminster, S.W.1, England, not later than April 30, 1960.

Assistant Residencies in Baltimore.

Two assistant residencies in internal medicine will be available from July 1, 1960, at The Hospital for the Women of Maryland, Baltimore, U.S.A. The hospital is Johns Hopkins affiliated, and specializes in graduate and post-graduate education. The full-time departmental head is the Johns Hopkins Associate Professor of Medicine. Applications should be sent to the Director of Medical Education and Chief of Medicine, The Hospital for the Women of Maryland, Lafayette Avenue and John Street, Baltimore 17, Maryland.

Royal Australasian College of Surgeons.

PRIMARY EXAMINATION FOR THE F.R.A.C.S.

A PRIMARY EXAMINATION in anatomy (including normal histology) and applied physiology and the principles of pathology will be conducted in Melbourne and Sydney in September, 1960.

The written papers will be held simultaneously in the two centres on Thursday and Friday, September 1 and 2, 1960. The examiners will visit the two centres for the purpose of conducting the *viva-voce* sections of the examination, which will commence in Melbourne on September 5 and in Sydney on September 12, 1960.

The examination is reciprocal with the primary examination for Fellowship of the Royal College of Surgeons of England, the Royal College of Surgeons of Edinburgh and the Royal College of Surgeons in Ireland, or the primary examination in surgery of the Royal Faculty of Physicians and Surgeons of Glasgow and the College of Physicians, Surgeons and Gynæcologists of South Africa.

Each examination is open to graduates of not less than one year's standing of a medical school approved by the Council of the College for the purpose.

Candidates must submit evidence of their qualifications and date of acquirement thereof.

Forms of application for admission to the examination may be obtained from the Examination Secretary, Royal Australasian College of Surgeons, Spring Street, Melbourne, C.1, Victoria.

When entering for the examination, candidates must state whether they desire to appear before the Board of Examiners in Melbourne or Sydney.

The fee for admission or readmission to the examination is thirty guineas, plus exchange on cheques drawn on banks outside Melbourne. The fee must be forwarded with the form of application so as to reach the Examination Secretary at his office in Melbourne not later than July 20, 1960. It is stressed that entries close at the College office in Melbourne on July 20, 1960, and that late entries cannot be accepted.

Copies of the regulations governing examinations for fellowship are available on application.

FACULTY OF ANÆSTHETISTS: PRIMARY FELLOWSHIP EXAMINATION.

A PRIMARY EXAMINATION for the F.F.A.R.A.C.S. in anatomy, physiology, pharmacology and pathology will be conducted in Melbourne and Sydney in September, 1960.

The written papers will be held simultaneously in the two centres on Thursday and Friday, September 1 and 2, 1960. The examiners will visit both centres of the purpose of conducting the *viva-voce* sections of the examination, which will commence in Melbourne on September 5 and in Sydney on September 12, 1960.

The examination is reciprocal with the primary examination for fellowship of the Faculty of Anæsthetists of the Royal College of Surgeons of England.

Each examination is open to graduates of not less than one year's standing of a medical school approved by the Council of the College for the purpose.

Candidates must submit evidence of their qualifications and date of acquirement thereof.

Forms of application for admission to the examination may be obtained from the Examination Secretary, Faculty of Anæsthetists, Royal Australasian College of Surgeons, Spring Street, Melbourne, C.1, Victoria.

When entering for the examination, candidates must state whether they desire to appear before the Board of Examiners in Melbourne or Sydney.

The fee for admission or readmission to the examination is thirty guineas, plus exchange on cheques drawn on banks outside Melbourne. The fee must be forwarded with the form of application so as to reach the Examination Secretary at his office in Melbourne not later than July 20, 1960. It is stressed that late entries cannot be accepted.

Copies of the regulations governing examinations for fellowship are available on application.

PRIMARY EXAMINATION FOR FELLOWSHIP.

AT the primary examination for fellowship of the Royal Australasian College of Surgeons held in March, 1960, the following candidates satisfied the Board of Examiners and were approved: Leon Cebon, John Anthony Connolly, John Russell Dalton, James Russell Fergusson Downie, Andrew Keith Frazer, Frank James Ham, Peter Francis Hart, Bryan Hartley, John Salisbury Jose, John Herbert Mitchell, Cedrick Rupert Naylor, James Patrick O'Collins, Anthony Oliver Robertson.

FACULTY OF ANÆSTHETISTS: PRIMARY EXAMINATION FOR FELLOWSHIP.

AT the primary examination for fellowship of the Faculty of Anæsthetists of the Royal Australasian College of

DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA FOR THE WEEK ENDED FEBRUARY 27, 1960.[1]

Disease.	New South Wales.	Victoria.	Queensland.	South Australia.	Western Australia.	Tasmania.	Northern Territory.	Australian Capital Territory.	Australia.
Acute Rheumatism	3	3(2)	..	..	..	..	..	..	6
Amœbiasis	..	..	..	..	..	..	..	..	..
Ancylostomiasis	..	..	1	..	..	..	60	..	61
Anthrax	..	..	..	..	..	..	..	..	..
Bilharziasis	..	..	..	..	..	..	..	..	..
Brucellosis	..	1	..	..	..	..	..	..	1
Cholera	..	..	..	..	..	..	..	..	..
Chorea (St. Vitus)	..	..	..	..	..	..	..	..	..
Dengue	..	..	..	..	..	..	..	..	..
Diarrhœa (Infantile)	4(2)	14(13)	5(3)	..	..	1(1)	20	..	44
Diphtheria	..	..	..	..	..	..	..	..	..
Dysentery (Bacillary)	..	2(2)	5(3)	1(1)	4(3)	..	2	..	14
Encephalitis	..	..	..	..	..	..	..	..	..
Filariasis	..	..	..	..	..	..	..	..	..
Homologous Serum Jaundice	..	..	..	..	..	..	..	..	..
Hydatid	..	..	..	..	..	..	..	..	..
Infective Hepatitis	69(19)	22(13)	9(1)	7(4)	5(3)	1	1	1	115
Lead Poisoning	..	..	..	..	..	..	..	..	..
Leprosy	..	..	..	..	4	..	3	..	7
Leptospirosis	1	..	7	..	..	..	..	..	8
Malaria	..	..	1(1)	..	..	..	..	..	1
Meningococcal Infection	1	2(1)	..	..	..	..	..	..	3
Ophthalmia	..	..	..	..	11	..	..	..	11
Ornithosis	..	..	..	..	..	..	..	..	..
Paratyphoid	..	..	..	..	..	..	..	..	..
Plague	..	..	..	..	..	..	..	..	..
Poliomyelitis	2(1)	..	1	..	..	..	..	..	3
Puerperal Fever	..	..	..	..	..	..	..	..	..
Rubella	..	6(6)	..	1(1)	4(4)	..	..	..	11
Salmonella Infection	..	..	..	4(4)	..	..	..	..	4
Scarlet Fever	3(2)	11(5)	1	..	..	..	..	..	15
Smallpox	..	..	..	..	..	..	..	..	..
Tetanus	..	..	..	..	..	..	..	..	..
Trachoma	..	..	..	..	2(2)	..	2	..	4
Trichinosis	..	..	..	..	..	..	..	..	..
Tuberculosis	53(35)	4(4)	10(4)	5(3)	12(6)	2(2)	1	..	87
Typhoid Fever	..	..	..	..	..	..	..	..	..
Typhus (Flea-, Mite- and Tick-borne)	..	..	..	..	..	..	..	..	..
Typhus (Louse-borne)	..	..	..	..	..	..	..	..	..
Yellow Fever	..	..	..	..	..	..	..	..	..

[1] Figures in parentheses are those for the metropolitan area.

Surgeons held in March, 1960, the following candidates satisfied the Board of Examiners and were approved: Thomas Howard Allen, Richard Hugh Sheppard Connock, John Davenport, Ian Ronald Philpott.

Nominations and Elections.

The undermentioned have applied for election as members of the New South Wales Branch of the British Medical Association:

Stewart, Peter William, M.B., B.S., 1957 (Univ. Sydney), "Mannamite", Cootamundra, N.S.W.

Beard, David Henry, M.B., B.S., 1960 (Univ. Sydney), Manly District Hospital, Manly.

Tedder, Elizabeth, M.B., B.S., 1960 (Univ. Sydney), Eastern Suburbs Hospital, Cnr. Queens Park and York Roads, Bondi Junction.

The undermentioned have been appointed as members of the New South Wales Branch of the British Medical Association: Cheung, Yee-Tim Joseph, M.B., B.S., 1960 (Univ. Sydney); Corry, John Richard, M.B., B.S., 1960 (Univ. Sydney); Kern, Ian Barry, M.B., B.S., 1960 (Univ. Sydney); Lalak, Ivan John, M.B., B.S., 1960 (Univ. Sydney); Smith, Robert Henry, M.B., B.S., 1960 (Univ. Sydney); Wilson, John David, M.B., B.S., 1960 (Univ. Sydney); Adler, Edith Marion, M.B., B.S., 1959 (Univ. Sydney); Amos, Bernard John, M.B., B.S., 1959 (Univ. Sydney); Bracken, Barry Carsluith, M.B., B.S., 1954 (Univ. Sydney); Renwick, Stuart Buckle, M.B., B.S., 1959 (Univ. Sydney); Childs, Winifred, M.B., B.S., 1959 (Univ. Sydney); Crombie, Nickel, M.B., B.S., 1956 (Univ. London), M.R.C.S., England, L.R.C.P., London, 1956; Skellet, Helen Barbara, M.B., B.S., 1959 (Univ. Sydney); Poliver, Rudolph Rezso, Regional registration under Section 21A of the Medical Practitioners Act, Barellan Region.

The undermentioned have been elected as members of the South Australian Branch of the British Medical Association, qualifications being M.B., B.S., 1959 (Univ. Adelaide), unless otherwise stated: Fahy, Carlien Lorraine; Menachem, Thomas Arthur; Bockman, David; Bradtke, Walter John; Burnell, Richard Hugh; Clayer, John Reeves; Colquhoun, Harold George; Collins, Kenneth Ernest; Downey, Michael Seymour; Edwards, Robert George; Hocking, Ian Winston; Lipert, John Raymond; Loke, Wye Tuck; Rush, Gillian Mary; Saunders, Elizabeth Stuart; Wells, Peter; Welch, Ian Donald; Wise, Peter Hermann; Wangel, Anders Gustaf; Wigg, David Ross; Gun, Richard Townsend; Kinlough, Margaret Anne, M.B., B.S., 1957 (Univ. Adelaide); Lippett, Richard, M.B., B.S., 1956 (Univ. Adelaide); Rippert, Reinhart, M.B., B.S., 1957 (Univ. Adelaide); Dellow, Peter Glynn, M.B., B.S., 1956 (Univ. Adelaide); Baumgarten, Alexander, M.B., B.S., 1959 (Univ. Sydney).

Australian Medical Board Proceedings.

QUEENSLAND.

The following have been registered, pursuant to the provisions of Section 19 (1) (a) (c) of *The Medical Acts*, 1939 to 1958, of Queensland: Leonard, Ian Ferguson, M.B., B.S., 1959 (Univ. Adelaide); Gudenswager, Alan Ernest, M.B., B.S., 1958 (Univ. Queensland); Marinkovich, Nevin John, M.B., B.S., 1958 (Univ. Adelaide); Schonell, Malcolm Edward, M.B., B.S., 1958 (Univ. Queensland); Breitkreutz, Neville Arthur, M.B., B.S., 1959 (Univ. Queensland); Smith, Vincent George, M.B., B.S., 1958 (Univ. Queensland); Green, William John Stanley, M.B., B.S., 1959 (Univ. Queensland); Lukin, Gresley Francis, M.B., B.S., 1958 (Univ. Queensland); Jones, Arnold, M.B., Ch.B., 1957 (Univ. Birmingham); Hopkins, Paul Herbert, M.B., B.S., 1958 (Univ. Queensland); O'Regan, John, M.B., B.S., 1958 (Univ. Queensland); Lee, Shirley Dugmore, M.B., B.S., 1958 (Univ. Queensland); McGree, Maurice Dening, M.B., B.S., 1959 (Univ. Sydney).

Deaths.

The following death has been announced:

Howett.—Robert Anthony Howett, on March 19, 1960, at Edinburgh, Scotland.

Diary for the Month.

April 6.—Western Australian Branch, B.M.A.: Branch Council.
April 6.—Victorian Branch, B.M.A.: Branch Meeting.
April 7.—South Australian Branch, B.M.A.: Council Meeting.
April 8.—Tasmanian Branch, B.M.A.: Branch Council.
April 8.—Queensland Branch, B.M.A.: Council Meeting.
April 12.—New South Wales Branch, B.M.A.: Executive and Finance Committee; Organization and Science Committee.

Medical Appointments: Important Notice.

Medical practitioners are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Medical Secretary, 135 Macquarie Street, Sydney): All contract practice appointments in New South Wales.

South Australian Branch (Honorary Secretary, 80 Brougham Place, North Adelaide): All contract practice appointments in South Australia.

Editorial Notices.

All articles submitted for publication in this Journal should be typed with double or treble spacing. Carbon copies should not be sent. Authors are requested to avoid the use of abbreviations, other than those normally used by the Journal, and not to underline either words or phrases.

Authors of papers are asked to state for inclusion in the title their principal qualifications as well as their relevant appointment and/or the unit, hospital or department from which the paper comes.

References to articles and books should be carefully checked. In a reference to an article in a journal the following information should be given: surname of author, initials of author, year, full title of article, name of journal, volume, number of first page of article. In a reference to a book the following information should be given: surname of author, initials of author, year of publication, full title of book, publisher, place of publication, page number (where relevant). The abbreviations used for the titles of journals are those of the list known as "World Medical Periodicals" (published by the World Medical Association). If a reference is made to an abstract of a paper, the name of the original journal, together with that of the journal in which the abstract has appeared, should be given with full date in each instance.

Authors submitting illustrations are asked, if possible, to provide the originals (not photographic copies) of line drawings, graphs and diagrams, and prints from the original negatives of photomicrographs. Authors who are not accustomed to preparing drawings or photographic prints for reproduction are invited to seek the advice of the Editor.

Original articles forwarded for publication are understood to be offered to The Medical Journal of Australia alone, unless the contrary is stated.

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